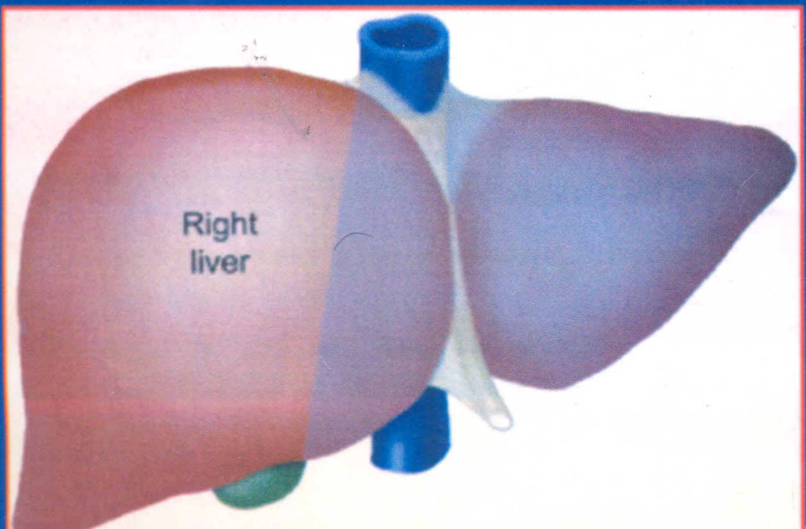
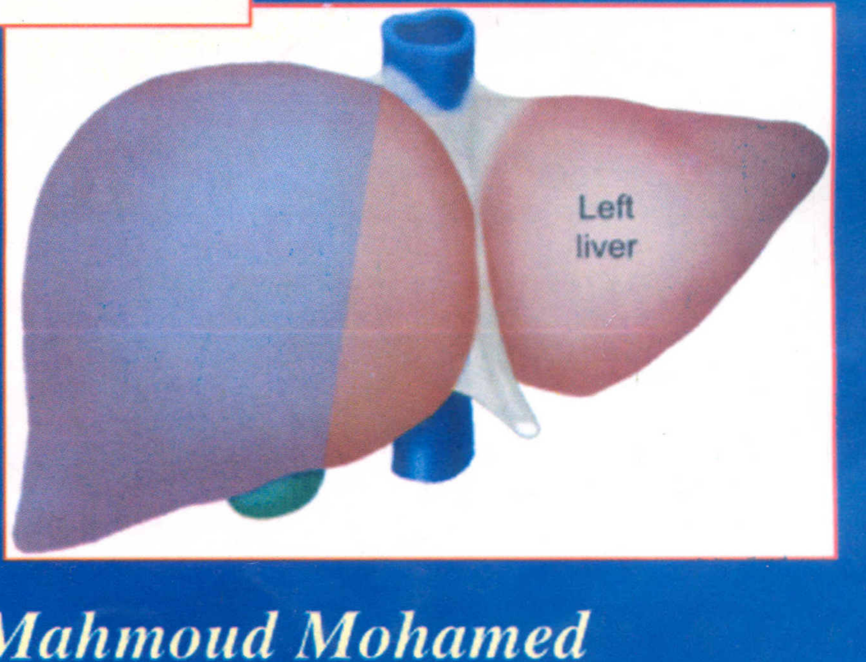
LECTURE NOTES OF INTERNAL MEDICINE

Hepatology





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The LIVER

Anatomy

- It is the largest and heaviest internal organ in the body (1200-1500gm).
- It is divided into left and right lobes by the middle hepatic vein.

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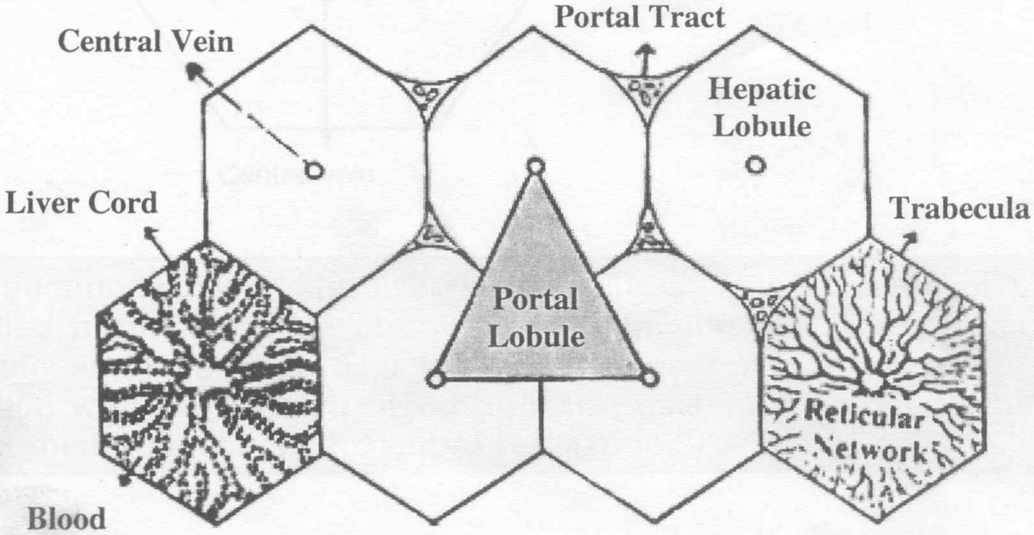
- The right lobe is larger and contains the caudate and quadrate lobes.
- The liver is further subdivided into a total of eight segments in accordance with subdivisions of the hepatic and portal veins, this permitting individual segment resection at surgery.



Histological structure of the liver

Histology

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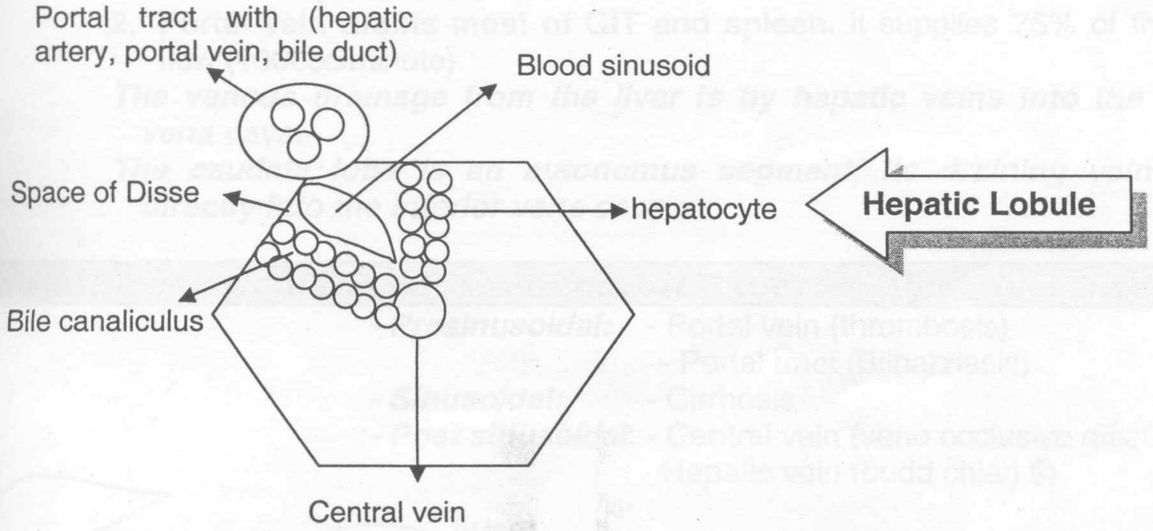
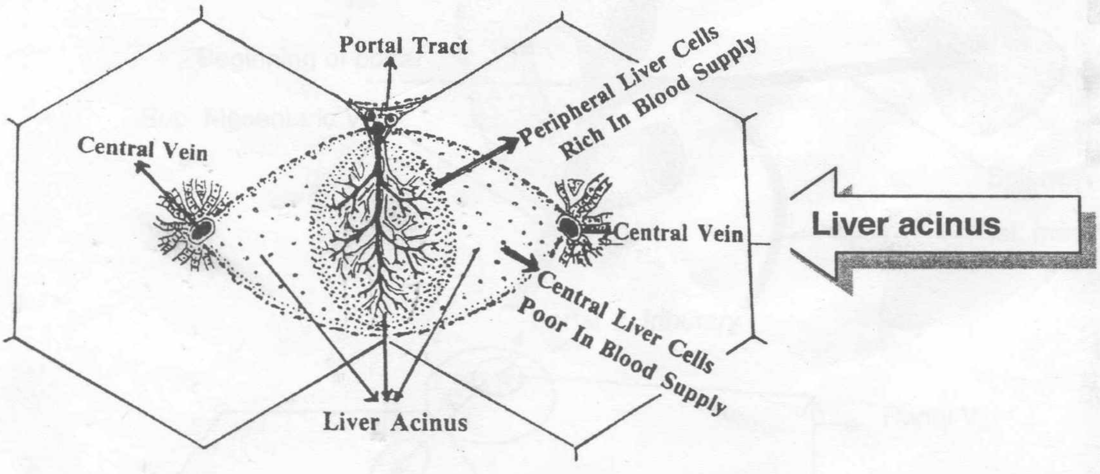
- The histological unit of the liver is the ***Hepatic lobule***
- Each lobule comprises a central vein, radiating sinusoids separated from one another by hepatocyte plates & peripheral portal tracts.
- In-between blood sinusoid & hepatocytes there is ***Space of Disse***.
  - This space contains connective tissue fibres.
- Also this space contains the ***"ito cells" or stellate cells*** responsible for vitamin A storage, vitamin D uptake and storage, collagen and extracellular matrix synthesis.
- Ito or stellate cells activation leading to production of collagen fibers.
- The sinusoids lack a basement membrane and are loosely surrounded by fenestrated endothelial cells and Kupffer's cells.
- ***Kupffer cells*** are derived from blood monocytes, they lie in the wall of sinusoids. They phagocytose damaged & aging RBCs, bacteria, viruses & immune complexes.

Stellate cells are contractile and may regulate sinusoidal blood flow. Endothelin and nitric oxide play a role in modulating stellate cell contractility. Activation of stellate cells produces collagen type I, III and IV.



The functional unit of the liver is the acinus. This consists of parenchyma supplied by the smallest portal tract containing portal vein radicle, hepatic arteriole and bile duct. The hepatocytes near this triad (zone 1) are will supplied with oxygenated blood and are resistant to damage than the cells nearer the terminal hepatic central vein (zone 3).


Portal Tract
Peripheral Liver Cells Rich In Blood Supply
Central Vein
Central Vein
Liver acinus
Central Liver Cells Poor In Blood Supply
Liver Acinus

Nerve Supply

The hepatic nerve plexus contains fibers from sympathetic ganglia (T_7-T_{10}), right and left vagi and the right phrenic nerve.

Blood supply to the liver and venous drainage

The blood supply to the liver constitutes 25% of the resting cardiac output and is via two vessels :

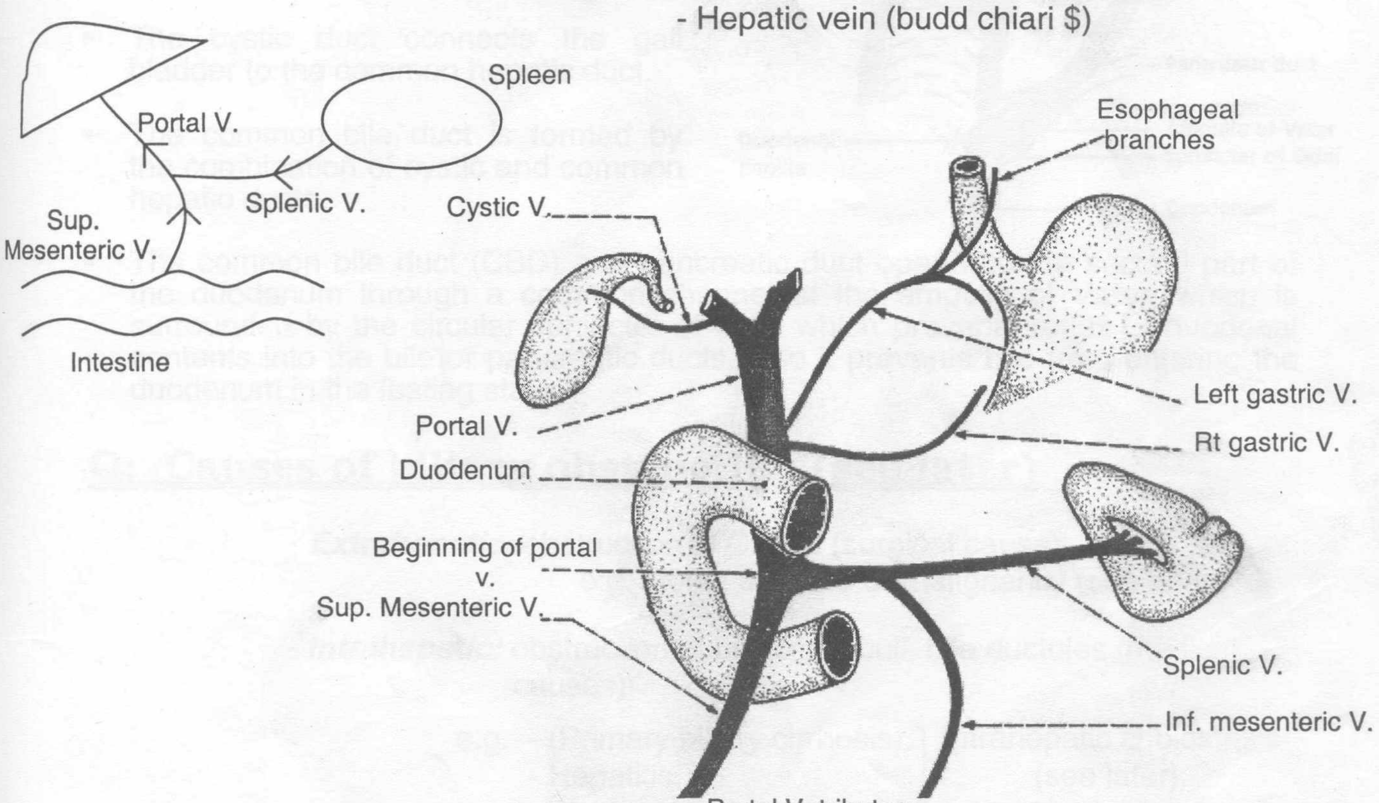
1. **Hepatic artery (Branch from celiac trunk),** it supplies 25% of the total blood flow (350cc/minute).
2. **Portal vein drains most of GIT and spleen.** it supplies 75% of the blood flow (1000cc/minute).

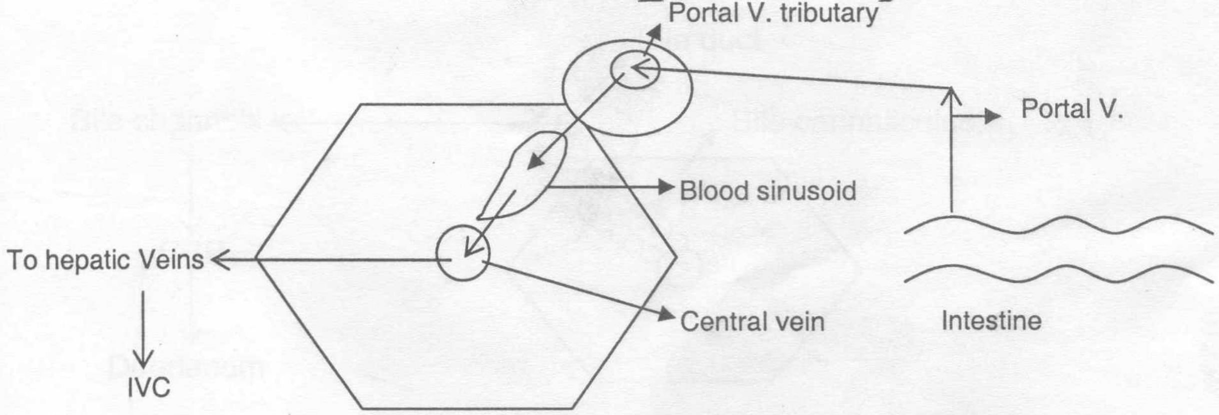
The venous drainage from the liver is by hepatic veins into the inferior vena cava.

The caudate lobe is an autonomus segment, its draining vein drains directly into the inferior vena cava.

Portal circulation and causes of portal Hypertension ? (see later)

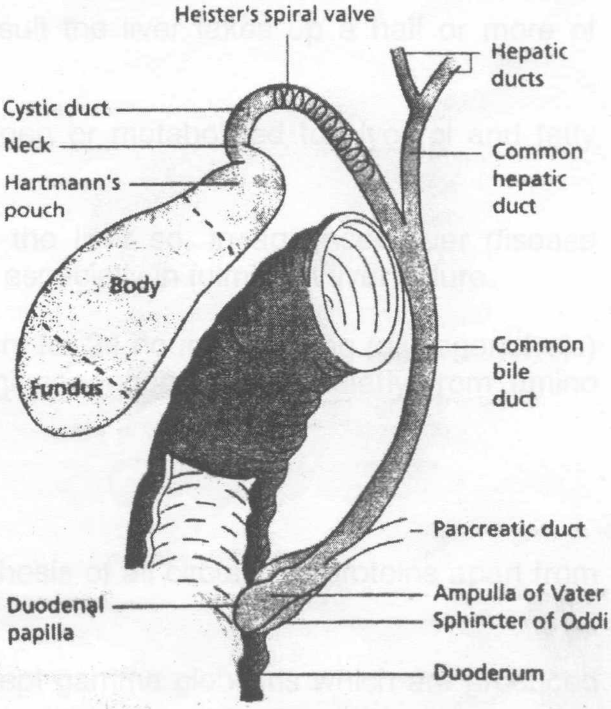
- Presinusoidal:	- Portal vein (thrombosis) - Portal tract (Bilharziasis)
- Sinusoidal:	- Cirrhosis
***- Post sinusoidal*:**	- Central vein (veno occlusive disease) - Hepatic vein (budd chiari $)





Lymph formed in the perisinusoidal space, is collected in lymphatics which are present in the portal tracts. These small lymphatics enter larger vessels which eventually drain into the hepatic ducts

Biliary system



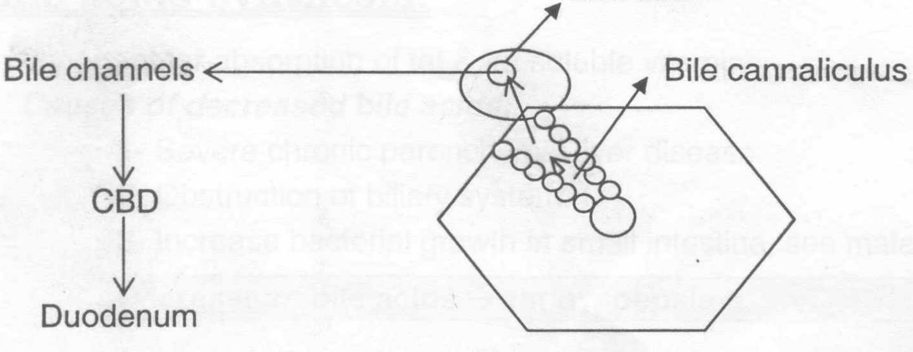
- Bile canaliculi join to form bile ductules near the portal tract, then enter the bile ducts in portal tracts.
- These then combine to form the right and left hepatic ducts that leave each liver lobe.
- The hepatic ducts join at the porta hepatis to form the common hepatic duct.
- The cystic duct connects the gall bladder to the common hepatic duct.
- The common bile duct is formed by the combination of cystic and common hepatic ducts.
- The common bile duct (CBD) and pancreatic duct open into the second part of the duodenum through a common channel at the ampulla of Vater, which is surrounded by the circular sphincter of Oddi which prevents reflux of duodenal contents into the bile or pancreatic ducts, also it prevents bile from entering the duodenum in the fasting state.

Q: Causes of biliary obstruction (see later)

- ***Extrahepatic:*** obstruction of C.B.D. (surgical cause):
e.g. stone, stricture or malignancy (see later).

- ***Intrahepatic:*** obstruction of bile canaliculi, bile ductules (medical causes):

e.g. - (Primary biliary cirrhosis). } Intrahepatic cholestasis
- Hepatitis. } (see later).



Biliary System

Liver Functions

1) CHO metabolism:

- Liver is rich in insulin receptors, as a result the liver takes up a half or more of glucose absorbed during feeding.
- The glucose taken up is stored as glycogen or metabolized to glycerol and fatty acids.
- About 70-80 gms of glycogen stored in the liver so, in advanced liver disease patients are liable to fasting hypoglycemia especially in fulminant liver failure.
- The glycogen stores (70-80 gm) is sufficient for 24 hours of fasting (glycogenolysis) after that glucose can be supplied by gluconeogenesis particularly from amino acids.

2) Protein metabolism:

- The liver is the principal site of synthesis of all circulating proteins apart from γ-globulins.
- Synthesis of albumin & globulin except gamma globulins which are produced in reticuloendothelial system.
- Also it synthesizes coagulation factors, complement, transferring, haptoglobin, caeruloplasmin, α_1 antitrypsin & α Feto protein.

3) Fat metabolism:

- The liver synthesizes (VLDLs) and (HDLs). Triglycerides are mainly of dietary origin but are also formed in the liver from circulating free fatty acids.
- Hepatic lipase removes triglyceride from (IDLs) to produce (LDLs) which are degraded by the liver after uptake by specific cell receptors. Cholesterol may be of dietary origin but most is synthesized from acetyl-CoA mainly in the liver, adrenal cortex and skin.

4) Bilirubin metabolism: (see jaundice)

5) Bile acids synthesis:

- Important for absorption of fat & fat soluble vitamins.
- ***Causes of decreased bile acids:***
    1- Severe chronic parenchymal liver disease.
    2- Obstruction of biliary system.
    3- Increase bacterial growth in small intestine, see malabsorption syndrome.

Decrease of bile acids → fat dyspepsia

6) Hormones and drugs:

- The liver is an important target site of hormone action e.g. insulin.
- Hormones are catabolized mainly in the liver e.g. insulin, growth hormone, oestrogens, & steroids.
- Cholecalciferol is converted to 25-hydroxycholecalciferol.
- Fat soluble drugs are converted to water soluble substances to facilitate their excretion in the bile and urine.

7) Storage

- The liver is the main site for storage of vitamin A, D & K.
- Also vitamin B12, folic acid and Iron are stored in the liver.

8) Immunological function

The liver acts as a sieve for the bacterial and other antigens carried to it through the portal vein from G.I.T., they are phagocytosed by Kupffer cells, these cells secrete interleukins and tumour necrosis factor (TNF).

Symptoms of Liver Disease

Acute liver disease

* This may be asymptomatic and anicteric.
* Symptomatic disease which is often viral produces fever, malaise, anorexia, pain in right hypochondrium.
* Jaundice usually occur due to intrahepatic cholestasis.

Chronic liver disease

* Patients may be asymptomatic.
* Patients may complain of non specific symptoms e.g. fatigue, but the following symptoms usually occur:
  - Pain in right hypochondrium, abdominal distension (ascites).
  - GIT bleeding (haematemesis and melena).
  - Pruritus due to cholestasis.
  - Ankle swelling, due to LL edema.
  - Confusion, drowsiness (hepatic encephalopathy).

Signs of Liver Disease

Acute liver disease

* Enlarged tender liver, jaundice.
* Spider naevi in severe acute disease e.g. fulminant liver failure.

Chronic liver disease

1. *Compensated liver:* spider navei, gynecomastia, parotid enlargement, clubbing, purpura, the liver is large or small, splenomegally.
2. *Decompensated liver:* foetor hepaticus, flabbing tremors, ascites, edema, jaundice.

- Acute liver disease e.g. acute viral hepatitis
- Chronic liver disease e.g. liver cirrhosis

LIVER INVESTIGATIVE TESTS

Investigations of liver diseases are classified into:

1. Liver function tests **(reflect functional state of the liver)**

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I- S. albumin (Marker of synthetic function)

serum

- Normal value =about 3.5 - 5 gm/dL.
- It has a fairly long half life (16-24 days)
- so decrease of serum albumin = chronic liver disease (liver cirrhosis, chronic hepatitis), also this reflects the severity of chronic liver disease.
- In acute hepatitis: serum albumin is initially normal. It may decrease later in severe cases.

II- Prothrombin time (PT)

Normal value = 10-14 sec., it is important to use INR (See haematology)

- Prothrombin is a protein synthesized in the liver, so it is also a marker of synthetic function.
- Its half-life is short.
- Therefore PT is very sensitive in acute & chronic liver disease.
  - Prolonged PT in acute viral hepatitis indicating fulminant liver failure.
  - Prolonged PT in chronic liver disease indicating poor liver function.
  - It becomes a very reliable test if repeated after vitamin K iv injection 10mg (to differentiate cholestasis from poor liver function).

Other uses of PT

1- Follow up of patients under oral anti coagulants.
2- Before liver biopsy (see later).

2. Liver Biochemistry

I- Test for hepatocellular damage (Aminotransferase or transaminases)

These enzymes present in hepatocytes & released in hepatocellular damage e.g. (hepatitis).

- ***SGOT 0-35 U/L (serum glutamic oxaloacetic transaminase) = AST***
  It is present in cytoplasm and mitochondria.
- ***SGPT 0-35 U/L (serum glutamic pyruvic transaminase) = ALT***
  It is present in cytoplasm only.

1. Aspartate aminotransferase (AST) or SGOT	2. Alanine aminotransferase (ALT) or SGPT
- Non specific, also increased in myocardial infarction.	- Specific, sensitive.
- Present inside mitochondria & cytoplasm.	- Mainly in cytoplasm.
- Shorter half life so its decline detects the onset of recovery e.g. in cases of acute hepatitis.	- Longer half life.

Examples:

1- ***Liver cirrhosis:*** there is mild rise of transaminases or normal enzymes. Also AST rise tends to be more than ALT.

2- ***Chronic hepatitis***

- Chronic active (severe form), usually there is rise 3 - 5 times the normal.
- Chronic persistent (mild form), usually there is mild rise or normal enzymes.

3- ***Acute hepatitis,*** there is marked rise up to > 20 folds. Also in acute hepatitis higher AST indicates more hepatocellular damage.

4- Increase in ALT is usually greater than AST in all hepatocellular damage e.g. hepatitis except alcoholic (see later).

II- Test for cholestasis

Alkaline Phosphatase (alk. P)

3-13 KA units / 100ml (old unit) OR 50-175 IU/L

Sources

a. Bone (osteoblastic activity).
b. Liver, from canalicular & sinusoidal membranes of hepatocytes.
c. Placenta.
d. Intestine.

In cases of biliary obstruction

Retention of bile salts → stimulation of hepatocytes → stimulates production and release of alkaline phosphatase (→ (↑ in blood) → rise 4-6 folds or more.

Usually alkaline phosphatase does not rise more than two folds in acute or chronic parenchymal liver disease

Causes of ↑ alkaline phosphatase

1. Biliary obstruction leads to marked rise.
2. Hepatic infiltration (leukemia, lymphoma,.....).
3. Hyperparathyroidism.
4. Hepatitis leads to mild rise.
5. Growing children, rickets.
6. Hepatic metastases.

- To confirm hepatic origin of alkaline phosphatase ask for the gamma glutamyle transferase (γGT) or 5 nucleotidase.
- γGT is more sensitive than alkaline phosphatase (appears in mild or early biliary obstruction).
- γGT elevated in alcoholic liver diseases, if γGT ↑ with normal alkaline phosphatase this may indicates alcohol intake.

- In parenchymal liver disease, the rise of transaminases is usually more than Alkaline phosphatase e.g. Hepatitis.
- In Biliary liver disease, the rise of alkaline phosphatase is usually more than transaminases.

Cholesterol (150-240 mg/dL) (Recommended < 200 mg/dL)

- Cholesterol is estrified in the liver & excreted within bile.
- So in obstructive jaundice there is high cholesterol.
- In primary biliary cirrhosis there is marked rise of cholesterol.
- In hepatocellular failure the ester form is decreased.

III- Total Plasma proteins and globulins

The total plasma proteins are about 6-8 gm/dL, and mainly composed of albumin and globulins, increase in total proteins is related to increase in globulins (gamma globulins) as in cases of multiple myeloma.

Serum immunoglobulins

- Normal value = about 2-3 gm/dL

Causes of rise of serum immunoglobulins (gamma globulins)

Polyclonal

1. ***Liver Cirrhosis:*** The increase of γ-globulins are due to reduced phagocytosis by Kuppfer cells of antigens absorbed from the gut, these antigens then stimulate Ab production by lymphoid tissue in L.N. and spleen. The total plasma protein is usually normal as the serum albumin is low.
2. ***Chronic infections***, e.g. chronic hepatitis, T.B.
3. ***Collagen diseases*** e.g. SLE.
4. ***Gammopathies*** as multiple myeloma (Monoclonal).

When gamma globulins are increased in liver disease ask for immunoelectrophoresis to determine the predominant Ab e.g.:

- IgG markedly increased in autoimmune hepatitis.
- IgA markedly increased in alcoholic liver disease.
- IgM markedly increased in primary biliary cirrhosis.

IV- Serum Bilirubin (see jaundice)

Normal value of total bilirubin is around 0.3-1 mg/dL.

Direct bilirubin (0.1-0.3 mg/dL), indirect bilirubin (0.2-0.7 mg/ dL)

a) Unconjugated hyperbilirubinemia

(When > 80% of serum bilirubin is unconjugated)

a) **Hemolysis:** There is evidence of hemolysis (↓ Hb, Reticulocytosis,….).

b) **Gilbert's syndrome (defective uptake)** with no evidence of hemolysis.

b) Conjugated hyperbilirubinemia:

(When > 5o% of serum bilirubin is conjugated)

a) **Obstructive**. (extra or intrahepatic).

b) **Hepatocellular** Jaundice.

to be differentiated by enzymes, liver function tests & other investigations.

c) **Dubin Johnson $ (defective secretion)**, there is no obstruction or LCF.

Increased serum bilirubin in liver disease

It is mainly due to intrahepatic cholestasis (swelling of hepatocytes) in acute liver disease, but if increased in chronic liver disease indicates impaired liver handling of bilirubin (decompensated liver).

3. Viral markers (See viral hepatitis)

4. Additional auto antibodies (See later)

5. Urine tests for bilirubin & urobilinogen (see Jaundice)

6. Tumor markers

- **α Fetoprotein**

Normal value < 25 ng/ml. (it sensitive but not specific)

It is made by fetal liver, it falls after birth.

Causes of ↑↑ α Fetoprotein

1. Hepatoma = marked increase > 400 ng/ml.
2. Hepatitis - liver cirrhosis.
3. Pregnancy in case of neural tube defect in the fetus.
4. GIT tumors and teratoma.

- **Des-γ-carboxy prothrombin** (it is specific but not sensitive)

It increases in cases of hepatocellular carcinoma.

7. Bromsulphthalein (BSP) Clearance Test

- Now it is very rarely used.
- This dye is injected I.V (5 mg/kg).
- 90% of the dye is cleared from blood by hepatic uptake and execration within 45 minutes.
- This test was used as a guide to hepatocellular function.
- A second recirculation peak occurs in Dubin Johnson syndrome (see later).
- Anaphylactic reactions may occur.

8. Urine Tests

- Dipstick tests are available for bilirubin and urobilinogen.
- Bilirubinuria is due to the presence of conjugated (soluble) bilirubin, it is positive in hepatobiliary disease.
- Positive urobilinogen in urine suggests haemolysis or hepatic dysfunction.

TESTS TO DETERMINE THE CAUSE OF PERSISTENT LFT ABNORMALITY

Diagnosis	Clinical clue	Initial test	Additional tests
Alcoholic liver disease	AST > ALT; ↑ GGT, ↑ MCV	Random blood alcohol	
Non-alcoholic fatty liver disease (NAFLD)	Metabolic Syndrome (central obesity, diabetes, hypertension)	Transaminases up to 300 U/l	
Chronic hepatitis B	Injection drug use, blood transfusion	Transaminases up to 300 U/l HBsAg	HBeAg, HBeAb HBV-DNA
Chronic hepatitis C		HCV antibody	HCV-RNA
Primary biliary cirrhosis	Raised alkaline phosphatase	AMA	
Primary sclerosing cholangitis	Inflammatory bowel disease	MRCP	ANCA antibody
Autoimmune hepatitis	Other autoimmune diseases	ASMA, ANA, LKM, transaminases 100-300 U/l	Immunoglobulin
Haemochromatosis	Diabetes/joint pain/pigmentation	Transferrin saturation, ferritin	HFE gene test
Wilson's disease	Neurological signs	Caeruloplasmin, transaminases 100 – 300 U/l	24-hr urinary copper
Alpha$_1$- antitrypsin	Lung disease	Alpha1-antitrypsin level	
Drug-induced liver disease	Drug/herbal remedy history	High transaminases	

IMAGING AND INVESTIGATIVE PROCEDURES

1) Plain X-ray:

1. 20% of gall stones are radio opaque.
2. Gases in biliary tract:
    - Gas producing organism (infection e.g. cholecystitis).
    - Fistula with intestine (biliary-enteric fistula).
3. Soft shadow of inflamed gall bladder, rarely calcification of gall bladder.

2) Oral Cholecystography (replaced by ultrasonic)

Idea:

Dye taken orally (iopanoic acid) → absorbed from intestine → liver uptake → excretion with bile → gall bladder → concentration in gall bladder leads to homogeneous opacification.

It is rarely required but may be useful as a test of gall bladder function.

Value :

1- Gall stone showing filling defect.

2- Function of gall bladder (concentration, evacuation)

- ***Concentration***: bad function means failure of gall bladder to opacify.
- ***Evacuation***: after fatty meal gall bladder will contract.

3- Non visualization will occur in jaundiced patient and in patient with liver disease (as the dye is excreted by the liver vial the same mechanism as bilirubin).

3) Sonar (Ultrasonography): **(Non invasive and safe)**

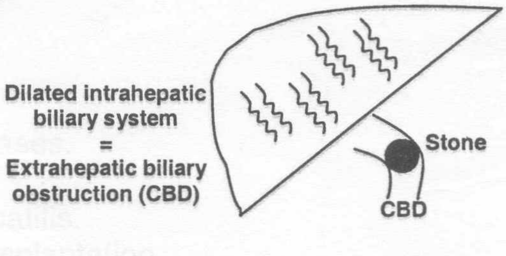
1- liver

1. Size.
2. Pattern of liver cirrhosis, periportal fibrosis (bilharziasis).
3. Focal lesions > 1 cm e.g. solid or cystic.
4. Portal vein diameter (normal around 13 mm, if > 14 = portal H) and patency.
5. Intrahepatic biliary dilatation in cases of obstructive jaundice.
6. Hepatic infiltration e.g. amyloidosis.

2- Spleen (measures the splenic size)

3- Ascites

4- Gall bladder


Dilated intrahepatic biliary system
=
Extrahepatic biliary obstruction (CBD)
Stone
CBD

1. Size.
2. Stone.
3. Thickness of its wall may be increased in chronic cholecystitis.

4) ERCP (Endoscopic Retrograde Cholangio Pancreatography)

Procedure

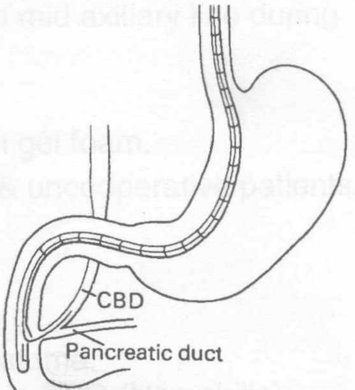
Through an upper endoscopy we cannulate ampulla of Vater with injection of dye in CBD & Pancreatic duct under screen.

Value:

1- Give an idea about extrahepatic biliary system,
    e.g. CBD   * Stone
                * Sticture – Ampullary carcinoma

2- Therapeutic ERCP, we can remove a stone from CBD, stent insertion through an obstruction.

3- Brachytherapy for cholangiocarcinoma.



Complications:

1- Injury.
2- Infection, give Ab. (3rd generation Cephalosporin).
3- Pancreatitis.

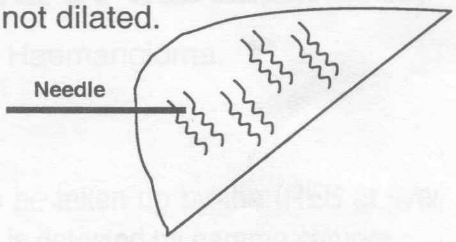
Indications:

Obstructive jaundice with intra hepatic biliary dilatation, to diagnose extrahepatic biliary obstruction.

Magnetic resonance cholangiopancreatography (MRCP) is a non invasive technique replacing diagnostic but not therapeutic ERCP.

5) PTC (Percutanous Transhepatic cholangiography)

- ***It is done*** through skin, we can introduce needle (skinny or chiba needle) into intrahepatic biliary system with contrast injection (guided by U/S). Success rate is reduced if the biliary system is not dilated.
- ***Value***: visualizes Intrahepatic biliary system, showing the biliary anatomy above the obstruction.
- ***Therapeutic***: If an obstruction in bile ducts is seen a bypass stent can be inserted.



In difficult cases PTC and ERCP are sometimes combined where PTC showing the biliary anatomy above the obstruction, and ERCP showing the more distal anatomy.

6) Liver biopsy

Indications

a. Unexplained elevation of transaminases.
b. Unexplained hepatomegally.
c. Focal lesion of the liver, chronic hepatitis.
d. Storage diseases, post-hepatic transplantation.

Precautions required for save liver biopsy

- PT must be not > 4 sec. above normal.
- Platelets > 100,000.
- Exclusion of bile duct obstruction or marked ascites.
- Cooperative patient.

Methods of liver biopsy:

(by trucut or Menghini needle through an intercostal space, in mid axillary line during expiration using local analgesia):

- Percutanous method.
- Percutanous method with plugging of the needle track with gel foam.
- Transjugular (as TIPS) for patient with bleeding tendency & uncooperative patients.
- Laparoscopic guided biopsy.

Complications:

- Injury.
- Intraperitoneal bleeding.
- Infection, Biliary peritonitis.
- Hepatic hematoma.
- Hemorrhage in CBD (Hemobilia).
- Intrahepatic A-V fistula.

Hemobilia produces biliary colic, jaundice and melena within 3 days of the biopsy.

The patient should be observed with pulse and blood pressure monitoring for the least 6 hours

Contraindications to liver biopsy

- Uncooperative patient
- Prolonged P.T > 4 seconds
- Platelets < 100,000
- Marked ascites
- Bile duct obstruction

Liver biopsy guided by ultrasound or CT is also performed particulary when specific lesions need to be biopsied

7) Liver angiography (coeliac angio, spiral CT has taken over)

Value: Vascularity of a focal lesion e.g - Hepatoma, Haemangioma.

/active

8) Radioisotope scan (^{99m}Tc)

Idea: Radioisotope technetium-99m is given IV to be taken up by the (RES of liver and spleen) then the radio activity of the liver is detected by gamma camera.

Value:
- Detect liver cirrhosis (diffuse low uptake) with ↑ uptake in spleen.
- Hepatoma gives a focal area with low uptake.

9) Fine needle aspiration (for cysts)

Cysts are either hepatic cyst or liver abscess (pyogenic or amoebic).

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10) Laparoscopy:

It gives view of the anterior & superior surface of the liver, gall bladder, spleen, & peritoneum, biopsy can be taken from diseased areas.

11) Endoscopy:

Upper GI endoscopy is used for the diagnosis and treatment of varices, and detection of portal hypertensive gastropathy or associated peptic ulcers. Also colonoscopy is used to detect portal hypertensive colopathy.

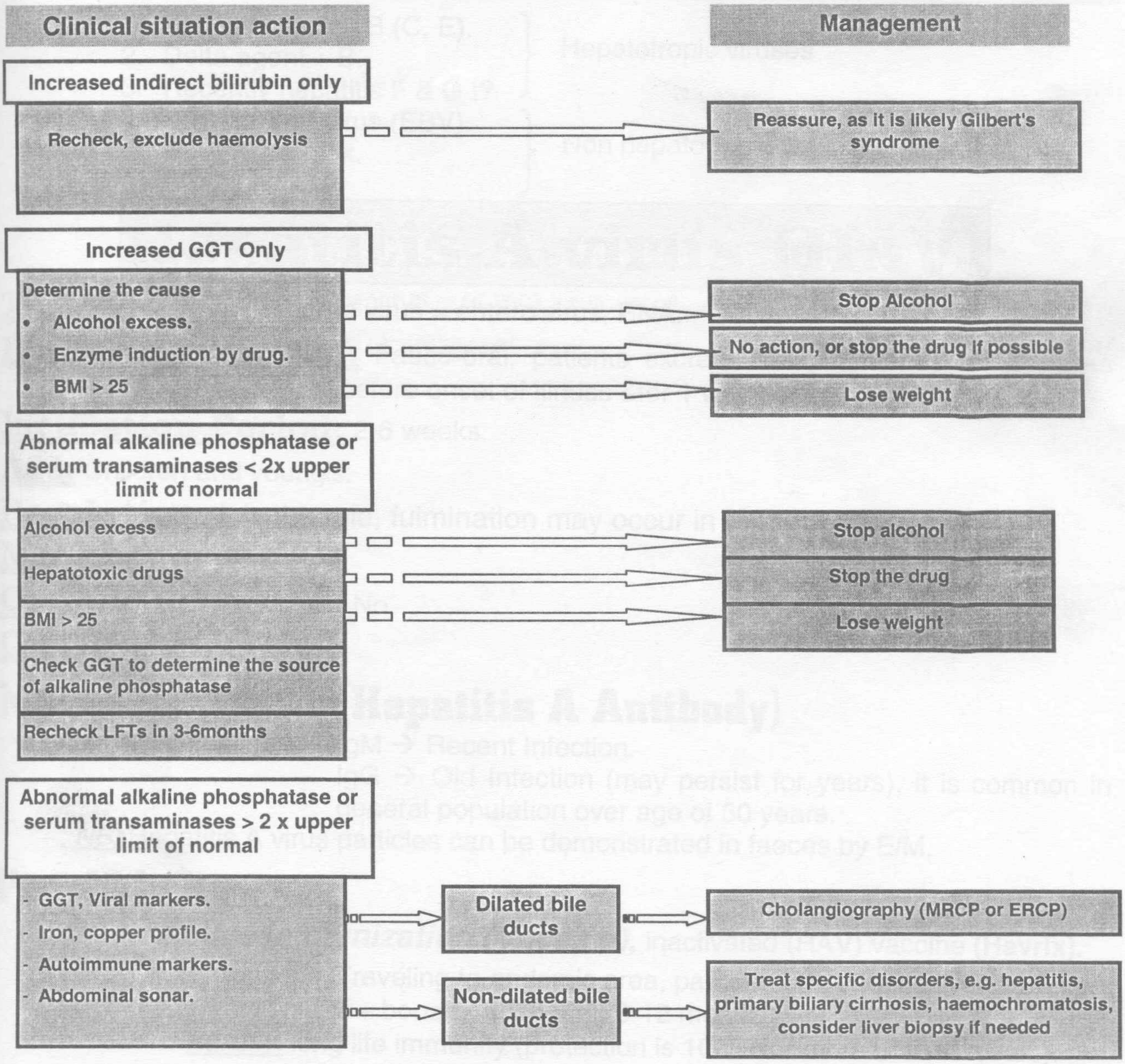
12) CT (computed tomography), for focal lesions of the liver

- o Spiral CT give more precise characters of a lesion and its blood supply. Spiral CT can differentiate malignant from benign lesions of the liver.
- o Visualization of pancrease, spleen, lymph nodes and lesions in porta hepatis.

13) MRI (Magnetic resonance imaging)

It is the most sensitive procedure for focal lesions of the liver, it can differentiate malignant from benign lesions. Also it provide angiography and venography.

[Management of abnormal LFTs in asymptomatic patients]


Clinical situation action
Management
Increased indirect bilirubin only
Recheck, exclude haemolysis
Reassure, as it is likely Gilbert's syndrome
Increased GGT Only
Determine the cause
• Alcohol excess.
• Enzyme induction by drug.
• BMI > 25
Stop Alcohol
No action, or stop the drug if possible
Lose weight
Abnormal alkaline phosphatase or serum transaminases < 2x upper limit of normal
Alcohol excess
Hepatotoxic drugs
BMI > 25
Check GGT to determine the source of alkaline phosphatase
Recheck LFTs in 3-6months
Stop alcohol
Stop the drug
Lose weight
Abnormal alkaline phosphatase or serum transaminases > 2 x upper limit of normal
- GGT, Viral markers.
- Iron, copper profile.
- Autoimmune markers.
- Abdominal sonar.
Dilated bile ducts
Non-dilated bile ducts
Cholangiography (MRCP or ERCP)
Treat specific disorders, e.g. hepatitis, primary biliary cirrhosis, haemochromatosis, consider liver biopsy if needed

ACUTE HEPATITIS

Definition: Inflammation of liver parenchyma for less than 6 months.

Causes

- Drug (Paracetamol, INH).
- Alcohol.
- Halothane hepatitis (Idiosyncrasy).
- Viral hepatitis.

Viral hepatitis is diagnosed by viral markers, while Non viral hepatitis is diagnosed by history and other investigations

CAUSES OF ACUTE VIRAL HEPATITIS

1. A, B, non A non B (C, E).
2. Delta agent + B.
3. Recently hepatitis F & G !?

} Hepatotropic viruses

4. Epstein Barr virus (EBV).
5. Herpes simplex.
6. CMV.

} Non hepatotropic viruses

Hepatitis A virus (HAV)

Type of virus: Picorna virus = entero virus, RNA.

Route of infection: Faeco-oral, patients excrete virus in faeces for 2 weeks before onset of illness &for 1 week after.

Incubation Period: 2-6 weeks.

Age: Children and young's.

Resolution: It is the rule, fulmination may occur in 0.5% of cases.

Malignancy: No.

Chronic hepatitis: No.

Carrier: No.

Markers: HA Ab (Hepatitis A Antibody)

if +ve = infection,
- IgM → Recent Infection.
- IgG → Old Infection (may persist for years), it is common in general population over age of 50 years.

NB: Hepatitis A virus particles can be demonstrated in faeces by E/M.

Prophylaxis:

1. ***Active immunization (Vaccine),*** inactivated (HAV) vaccine **(Havrix).**
   Indications: Traveling to endemic area, patients with chronic liver disease.
   Dose: 1ml/IM + booster dose after 6-12 month.
   Validity: long life immunity (protection is 100% for more than 10 years).

2. ***Passive immunization (Specific immunoglobulin)***

= immune serum globulin (Abs contain HA Ab).

Indication: (Sero prevention, Sero attenuation), efficacy is 80-90%.

- Contact = recent exposure (it is better to be given within 6 days of exposure).
- Traveling to endemic areas, it gives protection for 3-6 m.

Hepatitis B virus (HBV)

Type of virus: DNA virus.

Route of infection: (HBV is present in high concentration in blood so it is highly infectious).

- Blood, blood products.
- Sexual Intercourse, saliva.
- Transplacental (vertically). during delivery

Incubation Period: 2-6 months.

Age: Any (more in adult).

Malignancy: may occur.

Chronic hepatitis: 5%.

Flumination may occur.

Carrier: 0.5-10% (0.5% in USA & UK – 10% or more in Middle East).

Immune response and fate of hepatitis B infection:

Resolution: (competent immune system)

Good immune response → acute hepatitis followed by clearance of the virus and resolution.

Carrier (poor Immune response)

The cytotoxic T cells can't recognize the viral Ag leading to viral persistence. There is poor immune response so, no hepatitis and no clearance of the virus. The virus can proliferate with normal liver biochemistry and function.

Chronic hepatitis (5-10%): (Slightly better immune response)

Also the cytotoxic T cells can't recognize the viral Ag leading to viral persistence. There is better immune response so, chronic hepatitis occurs with no clearance of the virus with continuing hepatocellular damage.

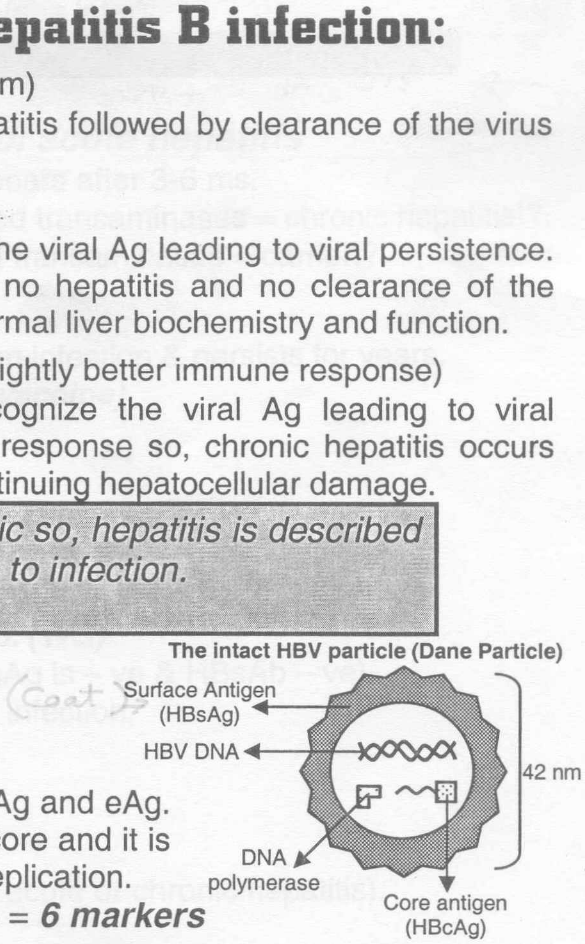
> *Virus A & B are not directly cytopathic so, hepatitis is described as T cell mediated immune response to infection.*
> *Virus C is cytopathic ??!!*

Markers:

The virus (Dane particle) consists of

1. ***Protein coat*** (surface Ag).
2. ***Core***: It contains DNA, DNA polymerase, core Ag and eAg. HBeAg is a protein subunit (part) of the core and it is secreted into plasma during active viral replication.

The intact HBV particle (Dane Particle)

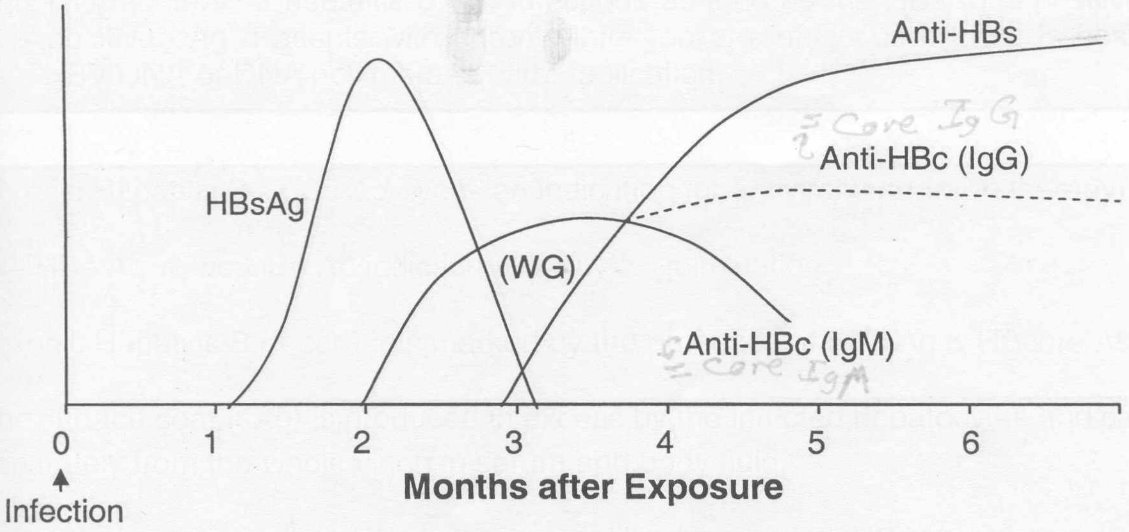


so, there are **3 antigens** + **3 Antibodies = *6 markers***

Surface (s) Ag + HBsAb

Core (c) Ag + HBcAb

HBeAg + HBeAb



HBsAg

- (It appears very early even before rise of enzymes).
- It appears in blood after 6 weeks up to 3 months after infection.

It is positive in the following conditions:

1. *Infection with HBV*.
2. *Hepatitis B*: - Acute (marked elevation of enzymes).
   - Chronic (mild elevation of enzymes).
3. *Carrier* (normal enzymes) (see later).

Cases of acute hepatitis with positive HBsAg are infectious.

Follow up of HBsAg in cases of acute hepatitis

- In acute hepatitis, HBsAg disappears after 3-6 ms.
- If persists for > 6 ms with elevated transaminases = chronic hepatitis!?.
- If persists for > 6 ms with normal transaminases = carrier!?.

HBs Ab

- Appears in blood after 3-4 months from infection & persists for years.

It indicates immunity (No need for vaccine)

- IgM = recent infection.
- IgG = old infection.

HB core Ag: It is present in hepatocytes (not in blood).

HB core Ab

- ***HB core Ab IgM + ve in window gap. (WG)***

  (Window gap = a period in which HBsAg is – ve & HBsAb – ve).
- HB core Ab IgM also indicates recent infection.
- If +ve HBcore Ab IgG = past infection.

HBe Ag

- ***If +ve = Active viral replication.***
- ***Also it indicates high Infectivity*** (in acute or chronic hepatitis).

HBe Ab

- ***= Low infectivity.***
- ***= Convalescence.***

Patients with acute viral hepatitis B are infectious as long as the HBsAg is positive or there is positive eAg. Patients with chronic infection are infectious if there is positive HBeAg, HBV DNA or DNA polymerase (viral replication).

- Chronic Hepatitis B+ HBe Ag +ve is an indication for antiviral (interferon therapy).
- +ve HBe Ag + –ve HBe Ab indicating liability for fulmination.
- Chronic Hepatitis B or carrier is marked by the presence of HBs Ag & HBcore Ab IgG
- The surface coat (sAg) is produced in excess by the infected hepatocytes and can exist separately from the whole virion in serum and body fluid.
- Carriers showing positive HBsAg, negative HBeAg, positive HBeAb with no HBV DNA in the serum. They have no evidence of active liver disease, also they are not highly infectious.
- Asymptomatic persons with positive eAg and HBV DNA can progress to active liver disease, it is better to consider that they have occult liver disease rather than being true carriers.
- Mutations of virus B occurs in chronic HBV carriers or can be acquired by infection. Also mutation occurs in patients with fulminant hepatitis and also following interferon therapy. Patients showing positive HBsAg and HBV DNA with negative eAg, Anti HBe may be positive or negative. So, HBeAg is less useful in detecting infectivity and HBV DNA must be measured.

Prophylaxis:

1- Vaccine: 10-20 μg IM (dose depends on formulation)

- It is made by recombinant DNA.
- أهم الطرق → It is given by IM injection 3 doses over 6 months (0, 1, 6) in deltoid.
- Each dose is 10 μg IM for **(Recombivax)** and 20 μg IM for **(Engerix).**
- It gives immunity in 90% of patients.
- To check vaccine, measure HBs Ab at 7-9 months after the initial dose.

Indications: (Risk group)

- Doctors, nurses. Patients with hemophilias.
- All newborn babies of HBsAg-positive mothers.
- Hemodialysis patients.
- Sexual parteners of HBsAg-positive patients

في الحقن (VACCIRA)

2- Immuno globulin (HBIG): hepatitis B immunoglobulin

(مصر حصل واللقاح زي مصيبات الكبد)

- It contains HBsAb.

Indication: Recent exposure. It should be given within 24 hours or at most a week from exposure to infected blood.

Hepatitis C virus (HCV)

Mode of infection

- It is a single stranded RNA virus of the flaviviridae family
- Mainly blood transfusion (90% of cases) i.e post transfusion hepatitis.
- The virus has low concentration in blood than HBV.
- Sexual transmission can occur but less than HBV, transplacental transmission is relatively uncommon, saliva can be also infective.

There are at least six genotypes of virus C, genotype I account for 70-80% of cases.

I.P.: 7-8 weeks

Chronicity: Occurs in more than 50% of cases.

Malignancy: May occur.

Carriers:!? 0.02% in Europe, 6% in Africa!?.

Markers:

HC Ab (by ELISA or RIBA method)

If +ve= infection, but it doesn't indicate immunity.
RIBA (recombinant immunoblot assay)

PCR (polymerase chain reaction)

If +ve = activity as it detect the RNA of virus in blood.
(recently PCR titre i.e. Quantitative method is available)

No vaccine is available for virus C

Hepatitis E virus (HEV)

- It is an RNA virus (Calcivirus)
- Mainly faeco oral.
- ***I.P.:*** 2-8 weeks
- ***Fulmination with pregnancy.***
- No chronicity.
- No carrier.
- ***Marker,*** HEV Ab (IgM, IgG), PCR.
- Vaccination may soon be available.

Hepatitis D virus (HDV) (Delta agent)

- Alone is not pathogenic as it is an incomplete RNA particle.
- It is activated by the presence of HBV, as its RNA particle enclosed in a shell of HBs Ag.
- ***Marker:*** anti Delta (IgM, IgG).
- ***Co-infection*** with HBV leads to acute hepatitis with +ve antiDelta IgM and HBc Ab IgM.
- ***Superinfection*** results in an acute exacerbation of chronic HBV, this is diagnosed by antiDelta IgM with HBc Ab IgG.

Fulminant hepatitis is more common with co-infection.

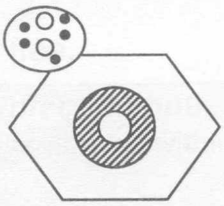
Hepatitis F, G

See later.

ACUTE VIRAL HEPATITIS

Pathology

Although some histological features are suggestive of aetiological factor, most of changes are essentially similar whatever the cause.



Features:

- Portal tract infiltration with inflammatory cells.
- Swelling of hepatocytes → narrowing of bile canaliculi → intrahepatic cholestasis.
- Centizonal necrosis (Zone 3).

Clinical picture

I. Non icteric hepatitis (Anicteric):

- It is usually a mild form of hepatitis, it may pass unnoticed.
- S bilirubin < 2.5 mg or < 3 mg.
- Clinically there is a mild flu-like illness with anorexia, nausea.
- Increased transaminases.

Fate

- Resolution, chronic hepatitis → post hepatitis liver cirrhosis !?

II- Icteric hepatitis:

A - Pre-icteric phase **(for about 1-2 weeks due to viremia)**

- Fever, headache, malaise.
- Marked anorexia, distaste for cigarettes.
- Pain in right hypochondrium.
- If you suspect you can confirm by rise of SGPT.

B- Icteric phase **(for about 3-6 weeks)**

Cholestatic Jaundice (Intra hepatic cholestasis)

Swelling of hepatocytes → obliteration of bile canaliculus → Intra hepatic cholestasis → jaundice.

- Dark urine.
- Clay stool.
- Improvement of fever, malaise, headache.

O/E

- Liver: mild++, Soft, tender (acute stretch of liver capsule).
- Spleen: mild ++ = RES hyperplasia in 10% of patients.

D.D. of just palpable spleen?
Typhoid – Infective endocarditis – Viral hepatitis – Brucellosis – Infectious mononucleosis

C- Post-icteric (convalescence)

- Improvement of general condition (symptoms & signs disappear gradually)
- SGOT ↓ with the onset of recovery.
- S. bilirubin ↓↓ but jaundice persists for a time as bilirubin has a high affinity to collagen fibers in sclera.
- After about 3-6 ms patients become clinically & biochemically free.

C/P of acute viral hepatitis almost the same in different types of viral infection but:

1- Acute hepatitis A is less severe than acute hepatitis B, and the illness is over within 3-6 weeks. Pronounced cholestasis may occur.
2- Acute hepatitis B is more severe than A, also serum sickness like syndrome may occur.
3- Most infection with acute HCV are asymptomatic, most of patients are diagnosed years later with evidence of chronic liver disease.

Complications (of hepatitis B,C)

I- Hepatic complications (2, 3, 4, 5 may occur with hepatitis A)

1- Chronic hepatitis (persistent elevation of transaminases for > 6 ms).

2- Fulminant hepatitis with rapid development of acute L.C.F. and encephalopathy (associated with prolonged PT).

3- Prolonged cholestasis due to unresolved swelling of hepatocytes.

(Normal or mild rise of transaminases, ↑ Alk. P, ↑ bilirubin), spontaneous recovery usually occurs.

4- Relapse may be.

- Clinically manifested
  or
- Biochemically evident

} Reassurance, spontaneous recovery usually occurs.

5- Post hepatitis $:

- There is normalization of enzymes but the patient still complaining.
- It may be subjective & psychogenic (not due to liver disease).
- There is easy fatigue, malaise and pain in right hypochondrium.
- Treatment is reassurance & follow up.

6- Hepatoma.

Unconjugated hyperbilirubinemia **(due to pre-existing Gilbert's $)** may be brought to light during follow up of viral hepatitis.

II- ExtraHepatic complications

1- Aplastic anemia, Henoch-Scholein purpura.

2- Lichen planus with hepatitis C.

3- Urticaria, arthritis, pancreatitis, cryoglobulinemia.

4- Immune complex glomerulonephritis:

- For example, viral Ag + Ab + C → immune complex glomerulonephritis.
- Hepatitis B leads to membranous glomerulonephritis, but hepatitis C leads to membranoproliferative glomerulonephritis.

5- Immune complex vasculitis

- Due to persistent HBs Ag as in carrier & chronic hepatitis leading to polyarteritis nodosa.

6- Polyneuropathy.

Extrahepatic complications are rare with hepatitis A but may include arthritis, vasculitis, glomerulonephritis and cryoglobulinemia

Investigations:

1) Urine

- it is a bed side test.
- Direct bilirubin appears in urine (bilirubinuria) early sign, due to cholestasis.
- Urobilinogen in urine is variable:
  - Early with marked obstruction → –ve urobilinogen in urine.
  - Late with relieve of obstruction → +ve urobilinogen in urine.

2) Liver function tests, Enzymes, markers:

- SGOT, SGPT showing marked elevation.
- S. albumin is normal.
- Alk. P is mildly elevated.
- γGT, 5 NT, showing mild elevation.
- PT → normal = good prognosis.
  → prolonged = bad prognosis.
- S. bilirubin is elevated (direct more than indirect).
- Viral markers as before.

Follow up:

1) SGOT, its 1/2 life is short, so its decline = onset of recovery.
2) Follow up is by SGPT to detect relapse.
3) Persistance of HBsAg for example = chronic hepatitis or carrier.

Sequence of lab investigations in cases of acute hepatitis

1. To prove hepatitis → elevated enzymes.
2. To prove acute hepatitis → marked elevation of enzymes,
   S. albumin is normal.
3. Functional state of liver → by PT.
4. Etiology → Markers.

Treatment: Non specific treatment

1. Rest: (it is advisable, but strict confinement to bed is not necessary)

Rest until the patient becomes clinically & biochemically normal. (especially when the serum bilirubin becomes normal).

- HA, rest for one month !?
- HB, rest for two months !?

2. Diet: *(Dietary measures are unhelpful)*

- High carbohydrate diet. (source of energy, more palatable).
- Low fat diet (as fat cause nausea, dyspepsia especially with cholestasis).
- Proteins, no restriction except with fulmination.
- glucose I.V. with marked anorexia or vomiting.

3. Steroids:

- No benefit, it may lead to exacerbation!.
- It may be used in some cases with prolonged cholestasis!?

4. Vitamins

5. Antiemetics e.g. Domperidone

6. Immunoprophylaxis

HA → Vaccine, immunoglobulin.
HB → vaccine, immunoglobulin.

No need for interferon therapy in acute viral hepatitis as it is a simple disease that can be overcomed by immune system. Interferon has been used in some acute cases of hepatitis C with some success!?

Recent forms of viral hepatitis

Hepatitis G (HGV)

- Originally there is GB hepatitis agent which was isolated from a surgeon (GB)
- It is RNA virus (flavivirus)
- Hepatitis GB virus is three types, (HGBV-A), (HGBV-B) and (HGBV-C)
- HGBV-C is similar to HCV
- Now HGBV-C and HGV are considered as the same virus
- HGV is transmitted parenterally and is found in I.V drug users, haemophiliacs and dialysis patients
- Any rise in serum transaminases after HGV infection can be explained by co-infection with another virus e.g. HCV
- Up till now there is no definite evidence that HGV leading to acute or chronic hepatitis !?

Hepatitis F:

Sporadic cause of fulminant hepatitis, existence is not fully established.

Acute hepatitis due to non hepatotropic viruses

*** CMV:** (See infections) :

- It causes acute hepatitis particularly in immunocompromised patients.
- Liver biopsy shows intranuclear inclusions and giant cells.
- The virus can be isolated from the urine.
- It can be treated by ganciclovir 5mg/kg/d for 14-21 days.

*** Infectious mononucleosis:** (See infections):

- It is caused by Epstein-Barr virus.
- Mild jaundice.
- Minor abnormalities of liver biochemistry.
- Clinical hepatitis is rare.
- Positive Paul-Bunnell or monospot test.
- The sinusoids and portal tracts are infiltrated with large mononuclear cells.
- No specific treatment.

*** Herpes simplex:**

This virus occasionally causes generalized infection in immunocompromised patients.

- There is marked elevation of liver enzymes.
- Liver biopsy show extensive necrosis.
- It can be treated with Aciclovir.

*** Yellow fever:**

This viral infection is transmitted by mosquite Aedes aegypti leading to acute hepatic necrosis. There is no specific treatment.

Toxoplasmosis may produce clinical picture simulating infectious mononucleosis with abnormal liver profile but monospot and Paul-Bunnel tests are negative.

CHRONIC HEPATITIS

Definition

Inflammatory disease within liver parenchyma more than 6 months. Chronic viral hepatitis is the major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma in the world.

Causes

1. ***Viral*** (B ± D, C).
2. ***Drugs***: e.g. α-methyl dopa, INH.
3. ***Autoimmune (e.g Lupoid hepatitis).***
4. ***Inherited diseases*** e.g. Wilson's disease, α_1 antitrypsin deficiency.

Pathological types

1- ***Mild form*** previously called chronic persistent hepatitis.
2- ***Severe form*** previously called chronic active hepatitis.

Mild form of chronic hepatitis

- Common, particularly following H.B. ***(it is previously called chronic persistent hepatitis).***

Clinical picture

- Asymptomatic, it may be discovered accidentally.
- Fatigue & pain in right hypochondrium, fat intolerance may occur.

Example of presentation:

Patient subjected to surgery → Preoperative Investigations → Abnormal liver enzymes (mild ↑ SGOT, ↑SGPT), which are persistently elevated with follow up.

- Patient is asymptomatic.
- Other investigations are –ve e.g. hepatitis markers.
- Sonar is normal or showing mild ++ of the liver.

} Unexplained and persistent elevation of liver enzymes is an indication of liver biopsy.

LAB

Mild elevation of transaminases, also positive viral markers may be present e.g. HBsAg.

Biopsy: Portal tract infiltration with inflammatory cells with no loss of architecture.

Treatment:

1- ***Reassurance.***
2- ***Follow up / 6m by enzymes. (SGPT).***
3- ***Avoid*** hepato toxicity – hepatic support e.g. silymarin - antioxidants.

If superinfection with virus D occurs, it results in flare up of previously mild form chronic HBV hepatitis.

D.D. Gilbert's syndrome & post hepatitis $.

Severe form of Chronic Hepatitis

Previously called chronic active hepatitis.

Clinical picture

- It ranges from mild **asymptomatic cases** up to frank **LCF** & **portal H**.
- It will be transformed to cirrhosis.
- It is mainly viral or autoimmune.

Features of hepatitis for > 6m

- Jaundice is slight or absent.
- The liver may be enlarged and tender.
- Constitutional symptoms (malaise, fatigue, low grade fever,.....).
- Cutaneous signs of chronic liver disease (see later).

Progression to cirrhosis

- LCF (liver cell failure).
- Portal H.

Extrahepatic manifestations of chronic viral hepatitis

- Polyneuropathy, arthritis or membranous glomerulonephritis with chronic hepatitis B. Cryoglobulinemia and membranoproliferative glomerulonephritis with chronic hepatitis C.

Extrahepatic manifestations of autoimmune hepatitis

- Polyarthritis.
- Hashimoto's thyroiditis.
- Autoimmune hemolytic anemia.
- Grave's disease.

Types of autoimmune hepatitis

1. Lupoid hepatitis (Type I)

- Positive ANA (antinuclear antibody).
- Positive antismooth muscle Ab.

2. Type II

- IIa → +ve LKM (Liver, kidney, microsomal Ab), common in girls with good response to steroids.
- IIb → +ve SLA (soluble liver antigen).

Investingations:

1. Enzymes: SGOT and SGPT usually increased up to 3-5 folds or more.

2. Serum albumin: usually normal, it is low in advanced cases.

3. Markers: for viral or autoimmune hepatitis e.g. HBsAg, HCAB, ANA, LKM.

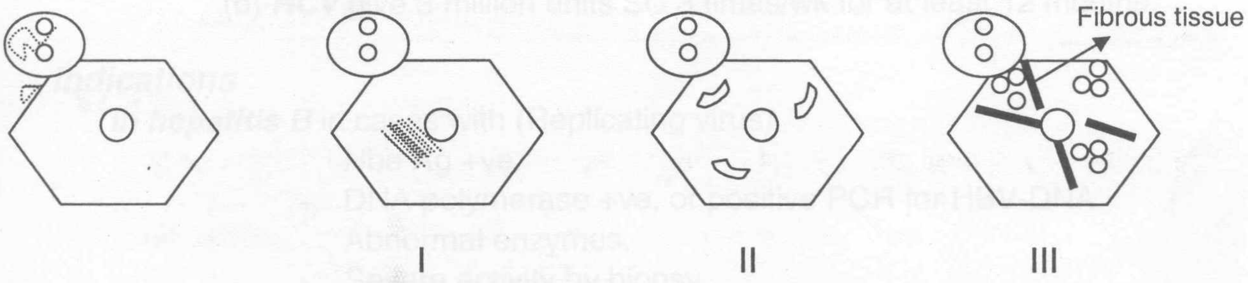
4. Biopsy:

The findings are:

I- Bridging necrosis (it is apoptosis rather than necrosis).

II- Piece meal necrosis.

III- Late, rosette appearance then cirrhosis.



- **In chronic hepatitis B, HBsAg may be seen as a ground glass appearance in the cytoplasm with haematoxylin and eosin staining, this can be confirmed with orcein staining.**
- **In chronic hepatitis C, lymphoid follicles are presents in postal tract.**
- **In chronic autoimmune hepatitis lymphoid follicles are less often seen than in hepatitis C, plasma cell infiltration is frequent.**

Treatment of chronic active autoimmune hepatitis

1. ***First and second week*** give prednisolone 30 mg/d (prednisone is converted to prednisolone in the liver).
2. ***Third week*** give 10-15mg/d.
3. ***Maintenance*** give 10-15 mg/d (for 6m).
4. ***Clinical + biochemical check every month.***
5. ***At 6th month, Liver biopsy is done:***
   - If there is full remission → continue maintenance treatment (restart if relapse occurs).
   - If there is no remission → Continue maintenance treatment + azathioprine (50-100 mg/d).
6. ***When to stop treatment?***

   Maintenance therapy with low dose prednisolone is required for at least 2 years after the following tests have become normal:
   - ANA –ve.
   - Normal transaminases.
   - Normal bilirubin.
   - Normal gamma globulin.
   - Inactivity by biopsy.

   So prednisolone therapy may extends over 2-3 years and usually longer, often for life to prevent relapse.

Treatment of chronic Active Viral Hepatitis

1- Conventional Interferon (Roferon®)

Dose

(a) ***HBV*** give 10 million units SC 3 times/wk for 4-6 months (usually for 16 weeks).

(b) ***HCV*** give 3 million units SC 3 times/wk for at least 12 months.

Indications

In hepatitis B in cases with (Replicating virus)

- Hbe Ag +ve.
- DNA polymerase +ve, or positive PCR for HBV-DNA.
- Abnormal enzymes.
- Severe activity by biopsy.

In hepatitis C: (it is given in combination with ribavirin, see later) in cases with.

- Positive PCR.
- Abnormal transaminases.
- Severe activity by biopsy.

- **The aim of interferon in hepatitis C is to eliminate the HCV RNA from the serum in order to :**
  - Stop the progression of active liver disease.
  - Prevent the development of hepatocellular carcinoma.
- **The presence of cirrhosis is not a contraindication but therapeutic responses are less likely.**
- **Patients with decompensated cirrhosis often have severe side effects and should be considered for transplantation.**
- **Pregnancy is a contraindication as interferon is teratogenic.**

Monitoring results of chronic hepatitis C:

* This is by measurement of aminotransferases, PCR at 3 months. If the enzyme and PCR remain abnormal, treatment should be stopped because a response to further treatment is unlikely.

* A sustained response is achieved in 40-50% at 12 months with genotype I and 80% in genotype 2 and 3.

* If PCR remains –ve 6 months after the end of treatment, relapse and histological progression are unlikely !?

Side effects:

1. Flu like illness occurring 6-8 hours after the first injection, it can be treated by paracetamol tab. 500 mg (1x3) (therapeutic dose of paracetamol is not hepatotoxic).
2. Myalgia, headache, treated by paracetamol tab. 500 mg (1x3)
3. BM depression, it is reversible.
4. Autoimmune thyroiditis, hemolytic anemia.
5. Myocarditis.
6. Depression.

Response

A) Chronic HBV

- Loss of HBeAg + appearance of HBe Ab.
- Loss of HBV DNA in blood by PCR.

B) Chronic HCV

- HCV → negative PCR.

- Transient rise in transaminases occurs at about 8 weeks due to lysis of infected cells.

II- Pegylated interferon (Pegasys®):

* Can be given once / wk for 48 weeks (180 μg S.C. /wk) in chronic hepatitis C genotype 1 and for 6 month for other genotypes.

* It is an interferon attached to polyethylene glycol to prolong half life.

* The dose for chronic hepatitis B is 100μg/wk for 4-6m.

Other Antivirals and immunostimulants

1. Ribavirin: Antiviral 200 mg tablets (Viracure®).

- The dose is 800-1200 mg/D, for genotype 1, 1800m for genotypes 2, 3, it is given with Interferon in treatment of chronic active hepatitis C.
- Side effects are hemolysis and hyperuricemia.
- Ribavirin is ineffective when used alone to treat chronic HCV.

2. Lamivudine (Xifax®) has activity against HBV (dose, 100mg/d for 1-2 years!?). It can be used as a monotherapy or combined with other antiviral drugs as interferon or ribavirin.

It can be given orally and is well tolerated, it is used in patients not responsive to interferon or if there is any contraindication to interferon (specially decompensated cirrhosis), mutation may occur during therapy, it can be treated with adenovir 10mg/day.

3. Levamisole (Ketrax®)

It is an immunostimulant, it may leads to seroconversion of HbeAg → HbeAb.

It may be useful if combined with antivirals.

Ursodeoxycholic acid may improve liver function in patients with chronic hepatitis

Prognosis of severe form chronic hepatitis

1- ***Autoimmune*** : Five year survival rate:
- without treatment is 50%.
- with treatment is 90%

2- ***Chronic viral hepatitis***

- The progression of the disease is slow.
- Active virus replication → cirrhosis.
- Hepatoma is liable to develop in the long term.

Predictive factors of a sustained response to treatment in patients with chronic hepatitis:

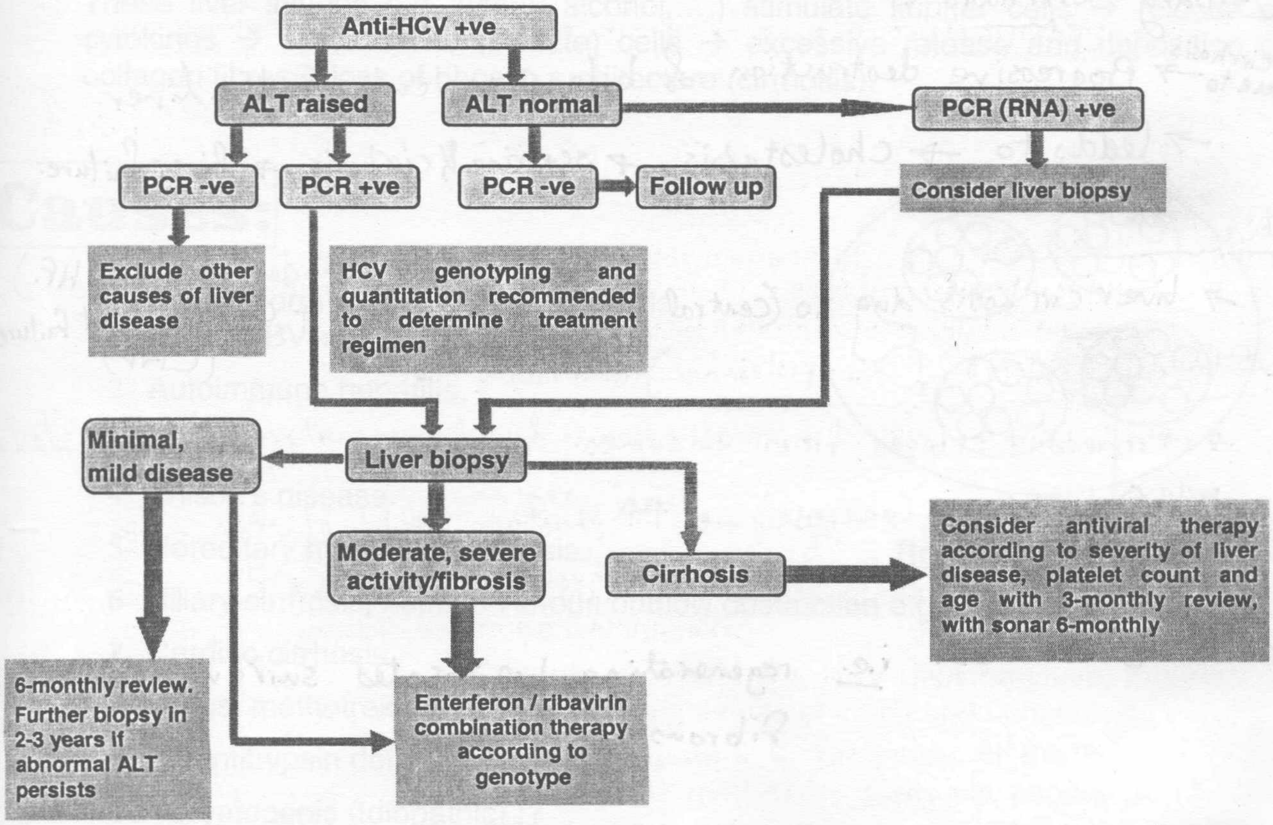
Chronic hepatitis B

- Short duration of disease.
- Active disease by biopsy.
- Negative delta virus.
- High transaminases.
- Low HBV DNA levels.
- Female gender.

Chronic hepatitis C

- Short duration of disease.
- Genotype 2 or 3.
- Young age.
- Low HCV RNA levels.
- Low hepatic iron stores.
- Low body weight.

Approach to a patient with hepatitis C


Anti-HCV +ve
ALT raised
ALT normal
PCR (RNA) +ve
PCR -ve
PCR +ve
PCR -ve
Follow up
Consider liver biopsy
Exclude other causes of liver disease
HCV genotyping and quantitation recommended to determine treatment regimen
Minimal, mild disease
Liver biopsy
Moderate, severe activity/fibrosis
Cirrhosis
Consider antiviral therapy according to severity of liver disease, platelet count and age with 3-monthly review, with sonar 6-monthly
6-monthly review. Further biopsy in 2-3 years if abnormal ALT persists
Enterferon / ribavirin combination therapy according to genotype

CIRRHOSIS

تليف / تشمع

Definition:

It is a chronic liver disease results from necrosis of hepatocytes followed by fibrous tissue deposition and formation of regenerating nodules with loss of hepatic architecture.

اختلال / تشويش

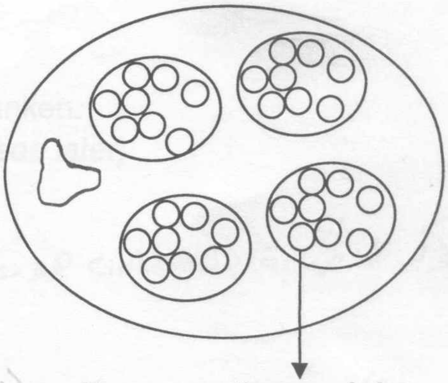
This derangement eventually produces portal hypertension and liver cell failure.

Liver cirrhosis constitutes the major response of the liver to a variety of longstanding inflammatory, toxic, metabolic or congestive insults.

Pathogenesis:

- Long standing injury to the liver lead to inflammation, necrosis and eventually fibrosis (initiated by activation of stellate cells).
- These liver injuries e.g. (virus, alcohol,….) stimulate kupffer cells → release of cytokines → stimulate ito (stellate) cells → excessive release and deposition of collagen fibres→ loss of hepatic architecture (cirrhosis).

Causes:



Regenerating nodules

→ Posthepatitis cirrhosis.

1- Severe form of chronic viral hepatitis HBV, HBV + D or HCV. most imp

2- Autoimmune hepatitis.

3- Alcohol. most imp

4- Wilson's disease. (copper overload)

5- Hereditary haemochromatosis. (iron overload)

6- Biliary cirrhosis, hepatic venous outflow obstruction e.g. Budd-chiari syndrome.

7- Cardiac cirrhosis.

8- Drugs: methotrexate.

9- α1 antitrypsin deficiency.

10- Cryptogenic (Idiopathic) !?

- When you describe the manifestations of liver cirrhosis you must comment on the cause and the presence of portal hypertension (PH) or liver cell failure (LCF).
- Regenerative nodules may be small (< 3mm, micronodular cirrhosis) which is a typical feature of alcoholic cirrhosis, or large (> 3mm, macronodular cirrhosis) which is termed "postnecrotic cirrhosis" following severe form of chronic hepatitis.

General Manifestations and Management of Liver Cirrhosis

Clinical picture

Symptoms:

Asymptomtic (no LCF, no PH) i.e. compensated liver cirrhosis.

Symptomatic

Cause: e.g.
- Haemochromatosis → (Bronzed D.M.)
- Wilson → extrapyramidal manifestations (Involuntary movement).
- Post-hepatitis (history of viral hepatitis).

LCF: Encephalopathy e.g. confusion, agitation (see later).

P.H.: Oesophageal varices → rupture → haematemesis or melena.
→ Congested spleen → splenomegaly.

Signs:

Cause

- Wilson's disease → extrapyramidal signs.
- Haemochromatosis → bronzed skin.

Cirrhosis

- ***Liver***: Firm, sharp border, nodular surface.
  Early, it is enlarged but late it is shrunken.
- ***LCF***: Flabbing tremors, Jaundice, ascites (see later).
- ***Portal H.***: splenomegaly (see later).

Investigations:

|biopsy| ← هو cirrhosis الذى يؤكد الاصابة بالـ

Liver tests and sonar:

- SGOT, SGPT → mild rise or normal.
- S. albumin, S. globulin ↑, PT (serum albumin and PT are indicators of liver function).
- Sonar:
  - Cirrhotic pattern.
  - Portal vein diameter increase in portal hypertension.

Cause: **(Type of cirrhosis)**

- Positive viral markers in cases of post hepatitis cirrhosis
- ↑Transferrin saturation, ↑ ferritin (Haemochromatosis).
- ↑Copper in urine, ↓copper in blood (Wilson's disease).
- Autoimmune markers (lupoid hepatitis), α_1 antitrypsin.

- *Biopsy to diagnose:*
  - Cirrhosis.
  - Cause: e.g. iron deposition in haemochromatosis.

→ Followup سؤال مهم

- ***Sonar and α–fetoprotein every 6 months to detect hepatoma early.***
- ***CT scan and MRI are useful to detect focal lesions and to discriminate benign from malignant lesions.***
- ***Endoscopy for detection of varices, gastropathy and colopathy.***

Treatment:

1- Cause e.g. Haemochromatosis give desferioxamine.

2- Treatment of L.C.F. and P.H. (See later)

3- Follow up with supportive treatment.

Classification of cirrhosis according to child functional classification (for prognosis)

	A	B	C
S. bilirubin	Less than 2 mg/dL	2-3 mg/dL	More than 3 mg/dL
S. albumin	More than 3.5 g/dL	3-3.5 mg/dL	Less than 3 mg/dL
Ascites	None	Mild	Advanced
Encephalopathy	-Ve	Mild	Advanced
Nutrition or nutritional status	Excellent	Good	Poor
PT (seconds prolonged)	< 4	4-6	> 6
prognosis	Good	Fair	Poor

The above classification helps you to:

1. Evaluate the functional state of the liver and the prognosis of patients.
2. Assess the operability for surgery especially for portal hypertension.

Child-pugh classification using the previous table without the nutrition item. They put the numbers 1, 2, 3 as a score instead of A, B, C. They calculate the scores as < 7 **(child's A)**, 7-9 **(child's B)**, > 9 **(child's C).**

Hereditary haemochromatosis

Definition: It is a disease characterized by increase of total body iron with excessive iron deposition in various organs including the liver, leading to functional organ failure.

Etiology: It is an autosomal recessive disease due to a mutation in gene (HFE) on the short arm of chromosome 6, leading to excessive iron absorption in small intestine exceeding the binding capacity of transferrin with deposition of excess iron in various organs.

↑↑↑ Absorption
↓↓↓ hepcidin

Mechanism of damage :

- The HFE gene protein interacts with transferrin receptor, which is a mediator in intestinal iron absorption. Iron is taken up by mucosal cells inappropriately exceeding the binding capacity of transferrin.
- Hepatic expression of hepcidin gene is ↓↓ decreased facilitating liver iron overload.

Clinical picture (Triad of bronze skin pigmentation, hepatomegally and DM).

- Males > females.
- Age around 40 yrs (slowly progressive).
- Excessive iron deposition in
  - *Liver* : cirrhosis → LCF, P.H. Hepatomegally is usually present.

    غالبا لا يكون في shrunken الكبد
  - *Heart* : Cardiomyopathy, with heart failure and arrhythmias **(The iron heart is a weak one)**.
  - *Pancreas* : DM.
  - *Skin* : bronzed color or leaden grey skin pigmentation in axillae, groins genetalia and in exposed areas (due to excessive melanin deposition).
  - *Hypofunction of gonads :* secondary to pituitary dysfunction.
  - *Joints* : Ca pyrophosphate deposition in joints (chondrocalcinosis), the relation of chondrocalcinosis to iron deposition is unclear.

Investigations

1. High serum iron - High serum ferritin (reflect tissue iron stores).
2. IBC is low.
3. Transferrin saturation is increased (it is accurate). normally about 33%
4. Increased blood sugar, liver biochemistry is often normal even with established cirrhosis.
5. sonar showing cirrhosis.
6. Biopsy (with prussian blue stain).
7. Computed tomography is suggestive, MRI is accurate.

- *Pigmentation + Cirrhosis, suspect haemochromatosis , primary biliary cirrhosis.*
- *Hepatocellular carcinoma is the main cause of death in haemochromatosis (complication).*
- *Each 500 ml blood contains 250 mg Iron.*
- *In hemochromatosis body iron reaches up to 60 gm (N = 5 gm).*
- *Mild degrees of parenchymal iron deposition in patients with alcoholic cirrhosis can cause confusion with haemochromatosis.*

Treatment

1- ***Venesection*** of 500 ml blood weekly until the serum iron is normal, this may take 2 years or more (160 units with 250 mg of iron per unit equals 40gm removed).
   - During venesection iron profile and MCV should be monitored.
   - When the iron profile becomes normal, three or four venesections per year are required to prevent reaccumulation of iron.

2- ***Chelator, desferrioxamine (desferal)***: used in patient who can not tolerate venesection because of cardiac failure or anemia.

3- ***Supportive treatment for the liver disease.***

4- ***Symptomatic treatment:***
   - DM give Insulin therapy.
   - Cardiomyopathy, see CVS.
   - Hypogonadism, give androgens (testosterone proprionate IM).

Screening:

In all cases, all first degree family members must be screened to detect early and asymptomatic disease. This can be done by transferrin saturation.

Primary (Haemochromatosis)	Secondary Haemochromatosis (i.e. Haemosidrosis)
- It is a hyperabsorptive malabsorption due to absence of the mucosal block for iron absorption in small intestine.	- It occurs in chronic haemolytic anemia + Multiple blood transfusion e.g. thalassaemia M.
- Inherited disease (autosomal R).	- Acquired disease.
- Iron deposition occurs in organ parenchyma (the functional unit of organ) → severe damage.	- Minimal damage, as iron is taken up mainly by RES.

- **MRI can differentiate as it shows that the pancreas is spared in secondary iron overload (haemosidrosis)**

Wilson's disease

(Hepatolenticular degeneration)

- Dietary copper (Cu) is absorbed from the stomach and upper intestine, then it is transported to the liver, where it is incorporated into ceruloplasmin (a glycoprotein synthesized in the liver) then it is released to the blood, Cu is also excreted with bile.
- The main abnormality of Wilson's disease is failure of both incorporation and biliary excretion of copper, also there is a low serum caeruloplasmin in 80% of patients.
- It is an autosomal recessive disease.

Clinical Picture

1- The liver

The liver disease varies from episodes of acute hepatitis which may progress to chronic hepatits or cirrhosis. Also fulminant hepatic failure may occur.

2- Cornea (Kayser Fleischer ring)

(Green brown ring of copper at corneoscleral Junction.) by slit lamp, early it is present at the upper periphery. It is absent in young children. It is due to deposition of copper in Descemet's membrane of the cornea.

3- Basal gangalia can be affected with extra pyramidal manifestations.

4- Renal tubular damage & hemolysis (mild).

5- Other changes: the lunulae of the nails are blue, also arthropathy may occur (chondrocalcinosis).

حالة متوقعة 2010

> *Recurrent acute hepatitis of unknown cause (e.g. –ve viral markers and autoimmune markers) in a patient under 40 years old suggests Wilson's disease.*

Investigations:

1- Sonar showing cirrhosis

2- Copper & caeruloplasmin are usually decreased in blood, they may be normal !?

3- Liver biopsy: deposited copper with especial staining.

4- Urine - May contain, glucose, aminoacids and phosphate (tubular damage).
- 24 hour urinary copper excretion is increased

5- Haemolysis and anemia may be present.

Treatment:

Cu Chelator:

- Long life treatment by penicillamine 1-2 gm/d oral → cupriuresis.
- Serious side effects of penicillamine may occur, zinc acetate 50 mg/TDS is safer.

Symptomatic: treatment of the extrapyramidal manifestations (neurological damage is usually permenant), supportive treatment for cirrhosis.

Liver transplantation: for decompensated cirrhosis or fulminant failure.

Alcoholic Liver Disease

Alcohol is the most common cause of liver disease in western societies.

Pathology

$$\text{Alcohol} \xrightarrow{\text{Alcohol dehydrogenase}} \text{Acetaldhyde} + H^+$$

- Acetaldehyde is direct hepatotoxic → hepatic injury.
- H^+ → disturbance in the NAD & NADH ratio → disturbance in carbohydrate & fat metabolism of hepatocytes with increased hepatic fatty acid synthesis with decreased fatty acid oxidation leading to hepatic accumulation of fatty acids that is then esterified to glycerides.
- Alcohol can enhance the effects of toxic metabolites of drugs e.g. paracetamol on the liver, as it induces microsomal metabolism via the microsomal ethanol oxidizing system (MEOS).

Presentations of alcoholic liver disease = Types of alcoholic liver disease

1- Fatty liver: (alcohol intake over months).

- Reversible after stoppage of alcohol, usually asymptomatic.
- - Liver ++, soft. It may be tender due to stretch of liver capsule.
  - Mild elevation of transaminases may occur.
  - Abdominal sonar is helpful (bright liver).
  - CT also will demonstrate fatty infiltration .

2- Alcoholic hepatitis (alcohol intake over longer periods).

Perivenular (zone 3) hepatocyte injury with ballooning & centrizonal necrosis + mallory hyaline + acute inflammatory cell infiltrate (mainly PNLs).

Clinical picture

Hepatitis with the following:

- Jaundice, malaise.
- Anorexia, nausea.
- Enlarged tender liver.
- Signs of chronic liver disease may occur.

Special diagnostic criteria (investigations)

1. γGT is very high.
2. SGOT/SGPT ratio > 2.

   This is because pyridoxine is essential for synthesis of SGPT rather than SGOT, alcohol → depletion of pyridoxine.
3. IgA is increased.
4. Macrocytosis of RBCs, leucocytosis.
5. Hyperlipidemia with haemolysis may occur (Zieve's syndrome).
6. Biopsy → Mallory hyaline in hepatocyte (characteristic but not pathognomonic).

3- Alcoholic cirrhosis as before plus:

Alcohol directly affects stellate cells, transforming them into collagen producing myofibroblast cells: cirrhosis will occur if there is an imbalance between degradation and production of collagen.

Special manifestations (alcohol is a vasodilator)

1. LCF. more prominant more than PH.
2. Marked palmar erythema.
3. Florid spider navei.
4. Hyperdynamic circulation, polyneuropathy.

- Alcohol liver disease becomes apparent at daily intake > 30 gm in men & > 20 gm in women more than 5 years, & usually more than ten years is required to produce alcoholic cirrhosis. The alcohol equivalents are: 30 ml of whisky, 100 ml wine or 250 ml bear contain (10 gm alcohol).
- Death in alcoholic liver cirrhosis due to complication of cirrhosis including hepatocellular carcinoma

Factors increase risk of alcoholic Liver disease:

1. Dose and duration. 2. ♀ > ♂.
3. HbsAg +ve. 4. Malnourishment.
5. HLA association or a genetic predisposition.
6. Immunological mechanisms have also been proposed.

Treatment

General Measures

- Patients should stop drinking, withdrawal symptoms (delirium tremens) can be treated with diazepam.
- Thiamine should be given to prevent wernicke – korsakoff encephalopathy.
- Rest, good nutrition, vitamins

(1) Fatty liver

- On stopping drinking alcohol the fat will disappear and the liver biochemistry usually return to normal.

(2) Alcoholic hepatitis

- Patients are advised to stop drinking for life.
- Vitamins B and C should be given by injection.
- Steroids (anti-inflammatory) can be used in absence of any infection.
- Treatment of encephalopathy.
- N-acetyl cysteine, pentoxifylline and liver support device are promising.

(3) Alcoholic cirrhosis

- Stop drinking for life.
- Supportive medications.
- Treatment of complication of liver cirrhosis.
- Liver transplantation.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is a chronic disease characterized by progressive destruction of bile ducts with intrahepatic biliary obstruction, eventually leading to cirrhosis.

Etiology & Pathology:

- It is unknown, but immunological mechanisms may play a role.
- Serum antimitochondrial antibodies are found in almost all patients.
- Also there is increased synthesis of IgM.
- There may be a decrease in T- suppressor cells which may allow cytotoxic T cells to produce damage to the bile ducts.
- There is granuloma and fibrosis of portal tracts with damage of the intrahepatic bile ducts (Intrahepatic biliary obstruction) leading to liver cirrhosis.

Clinical Picture (90% of patients are women 40-50 years)

(1) Manifestations of biliary obstruction

- Jaundice with dark urine, and clay stools.
- **Vit K** ↓ → bleeding tendency.
- **Vit D** → osteomalacia (**hepatic osteodystrophy**).
- **Itching:**
  - Is often the earliest symptom, may preceding jaundice by few years, central mechanism is suggested through an opioid substance released & acts on opiate receptors, this is proved by response to naloxone (Narcan).
  - Also itching is due to retention of bile salts.
- **Dyspepsia**
- **Pigmented xanthelasma** on eye lids or other deposits of cholesterol in the creases of the hands.

(2) Cirrhosis: with hepatomegaly is usually present.

Autoimmune disorders that may be associated with primary biliary cirrhosis are the sicca $, thyroid disease, autoimmune haemolytic anaemia, arthropathy and scleroderma.

Q Medical causes of Itching

1. Obstructive jaundice.
2. Primary biliary cirrhosis.
3. Cholestasis of pregnancy.
4. DM.
5. Renal failure.
6. Leukemia.
7. Hemolytic anemia.
8. Lymphoma.
9. Polycythemia rubra vera.

Investigations

(1) Biliary obstruction

a- ↑ Bilirubin (Direct).
b- ↑ Alkaline phosphatase.
c- ↑ γGT, 5' NT.
d- ↑ Serum cholesterol.
e- ↑ Serum transaminase (mild elevation).

(2) Autoantibodies

- **Antimitochondrial antibody** is present in over 95% of patients.

- Very high IgM.

(3) Sonar showing cirrhosis

(4) liver biopsy

Portal tract infiltrate with lymphocytes and plasma cells. 40% of cases have granuloma. Fibrosis of portal tracts with damage of the intrahepatic bile ducts.

Treatment (No specific therapy is available)

- Ursodeoxycholate (Ursofalk) 10-15 mg/Kg leads to improvement of liver enzymes and biochemical markers of cholestasis and jaundice (it should be given).
- Cholestyramine (10-15 gm/D) with breakfast (intestinal chelator of bile salts).
- Antihistaminics for itching & pruritis.
- Vit K (10 mg), vit D (100,000 unit IM) + Ca.
- Rifampicin, it inhibits hepatic reuptake of bile salt (enterohepatic circulation).
- Naloxone (an opioid antagonist).
- Immunosuppressive drugs e.g azathioprine has shown no clear benefit.
- Cyclosporine can be tried.
- Liver transplantation.

Secondary Biliary Cirrhosis

Cirrhosis can result from prolonged large duct obstruction (extrahepatic biliary obstruction) for months due to for example stricture of CBD, gall stones and sclerosing cholangitis. These conditions can be diagnosed by sonar, ERCP & PTC.

D.D of primary biliary cirrhosis:

- ***Sclerosing cholangitis***
    - Common in male. It is a chronic inflammatory disease of biliary system (intra & extrahepatic) with narrowing and obliteration of biliary channels.
    - AMA is negative but ANCA is positive.
    - It may be associated with ulcerative colitis.
- ***Other medical conditions presented with itching (see before).***

Q: Complications of liver cirrhosis

- PH.
- Ascites.
- H. encephalopathy.
- Hepatorenal syndrome.
- Hepatoma.
- Hepatic osteodystrophy.

Q: Post-Hepatitis Cirrhosis

Etiology: chronic hepatitis, viral, autoimmune or drug induced.
C/P: of cirrhosis (See before) + Past history of hepatitis.
Investigation & Treatment → see before.

Poor prognostic indicators in liver cirrhosis

Clinical

- Persistent jaundice
- Haemorrhage from varices
- Persistent hypotension
- Ascites
- Shrunken liver
- Encephalopathy

Lab

- Low serum albumin < 2.5 gm/dl
- ↑PT
- Low serum Na < 120 mmol/L
- High bilirubin

Liver Cell failure (LCF)

(Manifestations of decompensated chronic liver disease)

Causes **(Hepatocellular failure can complicate almost all forms of liver disease)**

1. ***Viral:*** B, C, B+ delta.
2. ***Drugs:*** α-methyl dopa, INH.
3. ***Alcohol.***
4. ***Autoimmune Hepatitis.***
5. ***Metabolic:*** Wilson, haemochromatosis.
6. ***Prolonged biliary obstruction & late malignancy.***

Clinical picture of decompensated chronic liver disease (LCF)

1- General failure of health: (Weakness, wasting & easy fatigability)

2- Fever (low grade) due to:

1. RES defect → Kupffer cells fail to clear bacteria from blood → Bactremia.
2. Increased level of ILI, TNF.

3- Jaundice (hepatocellular jaundice)

(Failure of liver to handle bilirubin), it is a sign of decompensation in chronic liver disease, but in acute liver disease it may be due to intrahepatic cholestasis.

4- Foetor hepaticus (sweetish, slightly faecal smell of the breath)

Due to mercaptans (which are absorbed from intestine) → by pass hepatic detoxication → excreted in mouth with breath. It is a sign of decompensation.

5- Ascites

(Causes of ascitis in chronic liver disease) i.e in liver cirrhosis

1. ***Hypoalbuminemia.*** (< 2.5-3 gms) due to ↓ synthesis.
2. ***Portal hypertension*** → it is a localizing factor rather than a cause, it leads to ↑ capillary pressure in splanchnic area (Portal H. alone dosen't lead to ascites).
3. ↑ ***Aldosterone*** (secondary hyperaldsteronism) due to hypovolemia & ↓ destruction of the hormone in the liver.
4. ↑↑ ***ADH*** (↑ production, ↓ destruction).
5. ***Non responsive kidney*** tubules to ANP.
6. ***Lymphorrhea:*** It occurs especially in post sinusoidal obstruction → Increase of lymph production with engorgement of lymphatics on the surface of liver with extravasation of lymph into peritoneum, **(weeping liver).**

6- Edema **(due to hypoalbuminemia, secondary hyperaldestonism)**

Causes of secondary hyperaldostronism:

-- ***Cardiac Edema*** due to cardiac failure → low COP, ↓ renal blood Flow

- ***Hepatic Edema***
- ***Renal Edema*** (Nephrotic)

} Hypovolemia → ↓ Renal perfusion

} Renal Ischemia ↓

(Secondary hyperaldosteronism) ← ↑ Renin

7- Haematological disorders

Anemia

- **Microcytic hypochromic:** iron deficiency due to chronic blood loss (esophageal varices & peptic ulcer).
- **Normocytic normochromic:**
  - hypersplenism.
  - toxic bone marrow depression.
- **Macrocytic normochromic:** see blood (macrocytic non megaloblastic anaemia).

Bleeding tendency

- Hypoprothrombinemia + hypofibrinogenemia + ↓ other coagulation factors.
- Decrease vitamin K dependant factors II, VII, IX, X (due to decrease production or due to cholestasis).
- Hypersplenism →thrombocytopenia.

(The Commonest cause of hypersplenism is portal hypertension)

8- CVS.

- Estrogen, nitric oxide (NO), prostaglandins, vasoactive intestinal peptide (VIP) are toxic vasodilators → hyperdynamic circulation.
- In advanced cases of LCF hypotension may occur.

9- Pulmonary manifestations (hepato pulmonary syndrome)

This syndrome represent hypoxia in patients with advanced liver disease without evidence of primary pulmonary disease due to:

- Opening of intra pulmonary A-V shunts (diagnosed by echo) → central cyanosis
- Opening of porto-pulmonary shunts
- Basal atelectasis and diffusion defect.
- Reduced pulmonary function due to ascites and pleural effusion
- Platypnea or orthodeoxia may occur.

Pulmonary hypertension may affect 2% of patients with portal hypertension, endothelin-1 may be related!?.

10- Endocrinal

There is disturbance of hypothalamic-pituitary function.

Failure of hormone metabolism may result in a rise in some hormones.

Female

- Amenorrhea & infertility.
- Atrophy of breast.

Male

- Female distribution of hair.
- Gynaecomastia.
- Impotence & ↓ libido.

11- Skin manifestations: (see clinical part)

- Spider navei.
- Palmar erythema
- Paper money skin.
- White nail **(Terry's nail)**.

12- Hepatic Encephalopathy

Definition: It is a neuropsychiatric complex in patients with liver cell failure. It occurs most often in patients with cirrhosis but also occurs in acute hepatic failure.

Types

- Acute hepatic encephalopathy in cases of acute fulminant hepatic failure.
- Hepatic encephalopathy in cases of liver cirrhosis, usually following precipitating factor.
- **Chronic portosystemic encephalopathy, due to spontaneous shunting in patients with portal hypertension.**

Clinical Picture and diagnosis:

(Diagnosis is mainly clinical, as routine liver biochemistry just confirm the presence of liver disease and not the presence of encephalopathy) e.g. high *PT,* low *albumin,* high *bilirubin* .

- ***Precoma***
    - Reversal of normal sleep rhythm.
    - Childishness, patient is irritable and confused.
    - Disturbed orientation, slurred speech (dysarthria), chorea, yawning, hiccough.
    - Excitement - abnormal behavior.
    - Foetor hepaticus.
    - Flapping tremors (asterixis).
    - Hyperreflexia, hypertonia.
- ***Coma:*** There is response to painful stimuli only

Recent Grades Of Hepatic Encephalopathy

Progression From hours to days

0 Subclinical decline of intellectual functions.

I Apathy + reversal of sleep rhythm, asterixis (flapping tremors) + confusion + agitation.

II Lethargy with response to verbal stimuli + asterixis.

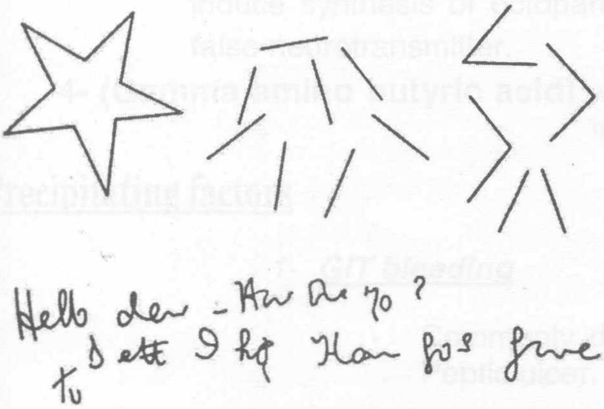
III Stupor with respond to vigorous stimuli + hyperactive reflexes + extensor plantar.

IV Coma, may respond to pain early, (Late no response to pain).

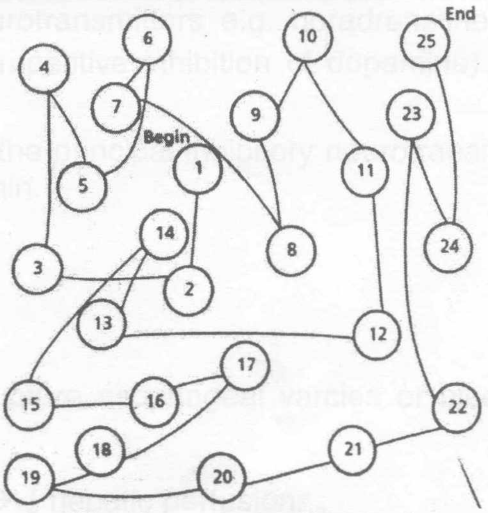
- Constructional apraxia is an early sign of hepatic encephalopathy (patient unable to draw a five pointed star).
- Reitan number connection test (patient unable to join numbers).

Additional investigations for encephalopathy:

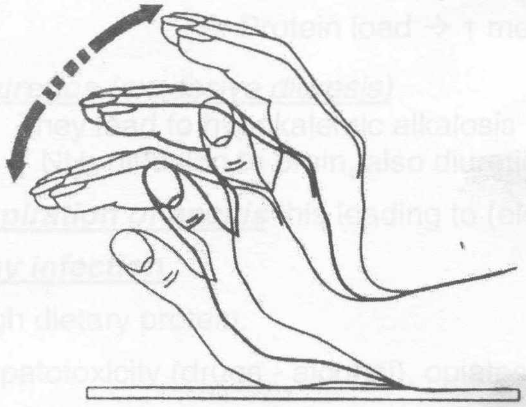
- EEG may show characterisitic abnormality, delta wave (slow with high amplitude).
- Visual evoked responses can detect subclinical encephalopathy.
- Arterial blood ammonia.


Hello dear - How are yo ?

Constructional apraxia test



Number connection test



Flapping tremors

Elicted by attempted dorsoflexion of the wrist with the forearm fixed

Mechanism of flabbing tremors (Asterixis)

It is a lapse in posture due to impaired inflow of joint and other afferent information to the brain stem reticular formation.

Pathogenesis

- Proteins → colon → bacteria flora act on proteins → metabolites (e.g. NH_3), they escape the liver detoxication and pass directly to the brain to produce hepatic encephalopathy.
- Metabolites escape from liver detoxication due to:
  1. Diseased liver.
  2. Liver is bypassed by the protosystemic shunts.

Metabolites

1- **NH3:** Ammonia decrease α-ketoglutarate leading to impaired the krebs cycle in neurons.

2- **Mercaptans**: inhibitory to CNS.

3- **False neurotransmitter** due to

- (↑ aromatic AA) e.g. tyrosine and phenylalanine.
- (↓ branched AA) e.g. valine, leucine and isoleucine.

Increase of phenylalanine and other aromatic AAs entry into brain results in decreased synthesis of normal neurotransmitters e.g. noradrenaline and induce synthesis of octopamine (competitive inhibition of dopamine) as a false neurotransmitter.

4- **(Gamma amino butyric acid)** which is the principal inhibitory neurotransmitter in the brain.

Precipitating factors

1- ***GIT bleeding***

- Commonly due to rupture esophageal varcies or bleeding Peptic ulcer.
- Bleeding → Shock → ↓ hepatic perfusion.

→ Protein load → ↑ metabolites → encephalopathy.

2- ***Diuretics (excessive diuresis)***

They lead to hypokalemic alkalosis → ↑ NH_3 production → ↑ NH_3 diffusion to brain, also diuretics lead to hypovolemia.

3- ***Aspiration of ascitis*** this leading to (electrolytes disturbance).

4- ***Any infection.***

5- High dietary protein.

6- Hepatotoxicity (drugs - alcohol), opiates, zinc deficiency.

7- Severe vomiting or diarrhea → electrolyte & acid base disturbances.

8- Spontaneous bacterial peritonitis.

9- Constipation.

10- Any surgical procedure.

DD of hepatic encephalopathy (↓level of consciousness + excitement) i.e. delirium

- Subdural haematoma.
- Delirium tremens (Alcohol withdrawal).
- Psychiatric disorder.
- Drunkenness.
- Hypoxia.
- Hypoglycemia.

Treatment

1- ***Control of precipitating factors.***

2- ***Diet (protein restrictions)***

- Protein intake should be maintained at 1gm/kg/d with transient reduction to 0.6gm/kg/d when needed in severe cases, then increase protein to the limit of tolerance as encephalopathy improves.

3- ***Eradication of bacteria flora (GIT antiseptic):***

- Rifaximin is unabsorbed and well tolerated for long time.
- Flagyl 200-250 mg/6 hours can be used especially with renal impairment.
- Neomycin (500 mg tab), 1-2 tab/6 hours, it is poorly absorbed and may cause nephrotoxicity and ototoxicity **(recently it should not be used).**

4- ***Systemic antibiotics e,g, third generation cephalosporines*** to eradicate any infection. e.g. specially spontaneous bacterial peritonitis.

5- ***Enema*** e.g. every 8 hrs or according to need.

6- ***Lactulose*** (duflak®) or lactilol more palatable (10-30 ml/8 hrs).

- It is a non absorbable disaccharide.
- It is an osmotic purgative → wash the bowels from nitrogenous substances.
- It is fermented into organic acid (H^+) → NH3 + H^+ → NH_4 (non absorbable), so low PH limits the danger of ammonia.
- The dose is adjusted to produce two semi-soft stools daily. It may lead to flatulence and diarrhea.

7- ***L-dopa*** → improves cerebral neurotrasmission or parlodel can be used as a dopamine agonist.

8- ***L-arnithine, L Aspartate*** (Hepamerz®): it decreases blood NH_3, zinc acetate 600mg/day.

Sedation must be avoided in cases of hepatic encephalopathy. If absolutely necessary (if the patient is violent), a small dose of a short acting benzodiazepine e.g. midazolam (Dormicum ®) may be given (flumazinel is ready for use as an antidote if needed).

Recent Trends in treatment of hepatic encephalopathy

1- Haemoperfusion → adsorption of toxins during passage of blood through an activated charcoal.

2- Bioartificial liver support **(see later)**.

3- Antibenzodiazepines e.g. flumazinel (Anexate®). It is GABA, benzodiazepine receptor antagontist.

4- Liver transplant.

Long term treatment of hepatic encephalopathy

1- Avoid precipitating factors

2- Increase protein diet to the limit of tolerance, 20-50 gm/day as the encephalopathy improves

3- Lactulose 10-30 ml/8 hours to avoid constipation (also avoid diarrhea)

Fulminant Hepatic Failure

- It is an acute liver failure with rapid development of hepatic encephalopathy within less than 8 wks in a patient without pre-existing Liver disease, to be distinguished from those instances in which hepatic encephalopathy represents an exacerbation of a chronic liver disease. Subacute hepatic failure refers to a slower paced illness.

Causes

1. ***Viral:*** A (0.5%), E (with pregnancy), B, C, B + delta.
2. ***Drugs***: Paracetamol Toxicity (>15gms=30tab), INH.
3. ***Alcohol***: toxicity, Amanita poisoning.
4. ***Acute fatty liver of pregnancy***
5. ***Reye's*** Child <5yrs (mortality 40-50%).
   It usually occur due to use of aspirin in a child with viral infection especially chicken pox.
6. ***Tetracycline*** (huge dose) IV especially during pregnancy
7. **Wilson's disease.**

Clinical picture: Acute encephalopathy with no precipitating factor, Manifestations as before + its complication as below.

Investigations

- High bilirubin – high PT.
- High transaminases, they are not useful indicators of the course of the disease because they fall with progressive liver damage
- Low serum albumin with progressive liver damage
- EEG showing the grade of encephalopathy
- Isotope scan of the liver may show no uptake
- Ultrasound showing liver size and evidence of underlying liver pathology
- Investigation to determine the cause e.g. viral and autoimmune markers, toxicology screen, copper levels

Treatment

A. Treatment of encephalopathy (as before)

B. Treatment of complications

1. **Hypoglycemia** (due to ↓ gluconeogenesis), give IV glucose infusion 10%.
2. **Hyponatremia** (due to ↓ free H_2O excretion).
3. **Hypokalemia** treated by KCl 10-15 gm/d.
   Hypokalemia is due to: - Diuretics.
   - Glucose infusion →insulin release→↓K^+.
4. **Hemorrhage** is due to decreased factors of coagulation, give Vit K, fresh frozen plasma or fresh blood and platelets.
5. **Infection** (septicemia) due to ↓ complement, give antibiotic.
6. **Brain edema** (due to disruption of BBB), give mannitol.
7. **Hepatorenal failure.**
8. **Lactic acidosis**, give $NaHCO_3$.

C. Transplantation and artificial liver support

- We can use bio-artificial liver support until the native liver recovers spontaneously or until a liver donor is available.
- Auxiliary liver translpantion also can be done giving the native liver time to recover and regenerate.

Artificial liver support?

- Haemoperfusion.
- Bio-artificial liver support i.e. passage of blood through permeable capillary tubes housed in a chamber containing viable cultured hepatocytes.
- Recently molecular absorbance recirculation system **(MARS)** is a device use non cellular technologies to mimic some aspects of liver function. Patient's blood circulates through a special hollow fiber filter with a membrane and protein (albumin) – bound toxins pass through membrane and attach to albumin in the dialysate compartment. The dialysate albumin is cleaned of toxins by continuously passing over charcoal and anion exchange resin columns and then recirculates. **MARS** impoves hepatic encephalopathy, reduces hyperbilirubinaemia and can also improve intractable pruritis.

Q: Treatment of chronic liver cell failure or chronic liver disease

- Diet – antioxidants.
- Vit K – hepatic support e.g. silymarin.
- Treatment of ascites.
- Management of portal hypertension.
- Treatment of encephalopathy and avoidance of ppt factors

Ascites

Ascites is the presence of excessive fluid in the peritoneal cavity

Causes of ascites

I- Straw-colored

- Malignancy. - Tuberculosis. -Spontaneous bacterial peritonitis **(Exudate)**.

- Cirrhosis.
- Constrictive pericarditis.
- Nephrotic syndrome.
- Mexedema
- Congestive heart failure.
- Meig's syndrome. (ovarian tumour with ascites and right pleural effusion)

} ***Transudate***

II- Chylous: Due to obstruction of main lymphatic duct by tumors.

III- Haemorrhagic

- Malignancy.
- Abdominal trauma.
- Rupture ectopic pregnancy.
- Acute pancreatitis.

Causes of ascites in absence of intrahepatic liver disease :

- Congestive heart failure.
- Peritoneal disease (TB, malignancy).
- Mexedema.
- Nephrotic syndrome.
- Budd Chiari.
- Acute pancreatitis.

Clinical Picture of ascites

Inspection:

- Generalized abdominal distension mainly in flanks.
- The umbilicus is everted and shifted downward.
- Distended abdominal wall veins due to portal hypertension or IVC obstruction.
- Widening of the subcostal angle, divarication of recti or hernia (e.g umbilical) due to ↑ intraabdominal pressure.

Palpation:

- Fluid thrill (fluid under tension).
- Liver and spleen may be felt by dipping method.
- Abdominal swellings may be felt in T.B. peritonitis and malignant ascites.

Percussion:

- Shifting dullness.
- Knee elbow method.

Auscultation:

- Puddle sign.
- Venous hum of portal hypertension.

Secondary effects of ascites:

- Right sided pleural effusion.
- The apex of the heart is displaced upward.
- Oedema usually follows the ascites.
- Congested neck veins.

Pathogenesis of ascites in liver cirrhosis

- ***Sodium and water retention*** occur due to peripheral arterial vasodilatation with reduction in the effective blood volume, this activates rennin-angiotensin system leading to salt and water retention. Nitric oxide and prostaglandins are the postulated causes of the vasodilatation.

- ***Portal hypertension (a localizing factor):*** Portal hypertension exerts a local hydrostatic pressure and also leads to increased hepatic and splanchnic production of lymph and transudation of fluid into the peritoneal cavity.
- ***Low serum albumin*** leading to reduction in plasma oncotic pressure.

Theories of Cirrhotic Ascites

The accumulation of ascitic fluid represents a state of total body sodium & water excess but the event that initiates this imbalance is unclear. Two theories have been postulated:

1. Underfilling theory:

Loss of fluid into peritoneum as ascites developed → decrease the intravascular volume (ineffective intravascular volume) → release of renin, aldosterone and ADH → Na and water retension → ↑ ascites formation.

2. Overfilling theory:

Systemic vasodilatation → excessive renal reabsorption of Na and water → hypervolemia → overflow of fluid into peritoneum.

Investigation

1- Cause: liver function tests – kidney function tests – Abdominal sonar – echocardiography.

2- laparoscopy: for peritoneal tumors or TB (biopsy can be taken).

3- Tapping: (the ascetic fluid is examined as follows)

- Bacteriology, Culture & sensitivity + Zeihl-Neelsen stain.
- WBC count and amylase level of ascetic fluid.
- Cytology for malignant cells.
- Chemistry for protein content (the serum albumin must be used as a reference point as below).

Exudate	*Transudate*
Inflammatory	Part of a generalized edema
Protein > 3 gm/dL	Protein < 3 gm/dL
Cells ↑↑ - ↑ LDH	Cells ↓↓ - ↓ LDH
Specific gravity > 1018	Specific gravity < 1018

The albumin gradient

- Serum ascites albumin gradient (SAAG) has replaced the exudative/transudative Classification of ascites.
- SAAG is the difference between plasma albumin and ascetic fluid albumin.
- SAAG value of ≥ 1.1 gm/dl predicts a portal hypertensive cause (transudate). Values < 1.1 gm/dl are associated with neoplasm, T.B, bacterial peritonitis (exudate).

DD of cirrhotic ascites (as before)

- Malignant ascites.
- Constrictive pericarditis
- Ovarian tumour
- Tuberculous ascites.
- Budd chairi $
- Pancreatic ascites with pancreatitis.

Treatment of ascites secondary to liver cirrhosis

1. ***Rest in bed:*** This improves renal blood flow and leads to diuresis.

2. ***Salt & fluid restriction***: follow up by body weight, urine volume and abdominal girth. Reduce sodium intake to 88 mmol/D (2 gm/D NaCl) i.e no added salt diet. In severe cases sodium restriction to 22 mmol/D (0.5 gm/D NaCl) is necessary. Restriction of water intake to 0.5 – 1 L/day is necessary only if the plasma sodium < 125 mmol/L.

3. ***Diuretics***: (aim is to acheive weight loss, 500 gm/day if there is no peripheral edema, 1000 gm/day if peripheral edema is present). Start with aldactone 100mg/D, if there is poor response add 20-40 mg lasix, increase dosages every 4-5 days up to 400mg/d aldactone + 160mg/d lasix.

   a) *Spironolactone* (Aldactone®) (100 mg daily upto 400 mg).

   - It is K sparing diuretic.
   - Also it is an aldosteron antagonist, if gynecomastia occur, amiloride 10-15 mg/d can be substituted.

   b) *Aldactone*® + *frusemide* (Lasix®) (40 mg daily up to 120-160 mg/d) if the patient is refractory to aldactone alone.

- **Side effects of loop diuretics are hyponatremia, hypokalemia and volume depletion.**
- **Ascitic fluid is mobilized more slowly than interstitial fluid so, diuretic should be used with care in patients without peripheral edema.**
- **Diuretics should be stopped in the following conditions :**
  - ◆ Rise in serum creatinine (pre renal failure) !?
  - ◆ Hyponatremia i.e. Na < 128 mmol/L (failure to clear free water)
  - ◆ Hypokalemia or hepatic encephalopathy.

4. ***Salt Poor Albumin:*** IV to increase the oncotic pressure of plasma.

5. ***Therapeutic abdominal paracentesis:***

   - Indicated if ascites is causing respiratory distress, also it is used as a means of rapid therapy in patients with ascites and peripheral edema.
   - Not > 2-3 L/session + replacement by IV albumin (6 -10 gm /for each liter of ascitic fluid).
   - Replacement is done to prevent re-accumulation and electrolyte disturbance.

   - ***Complications of paracentesis***

   1- Hypovolemia as the ascites reacumulates at the expense of the circulating volume.
   2- Encephalopathy due to electrolyte disturbance.
   3- Hepatorenal syndrome.

- ***Criteria of patient for safe therapeutic paracentesis i.e. to avoid complications:***
  - Tense ascites
  - Child's grade B
  - Serum bilirubin < 10 gm/dL
  - Serum creatinine < 3 mg/dL
  - Lower limb edema
  - Prothrombin > 40%
  - Platelet > 40,000/mm^3
  - Urinary sodium > 10mmol/24hours

Volume removed: 2-3 litres/session with albumin 6-10 gm/litre removed.

If Ascites is resistant or refractory to the previous measures, *the following causes must be considered and treated if possible:*

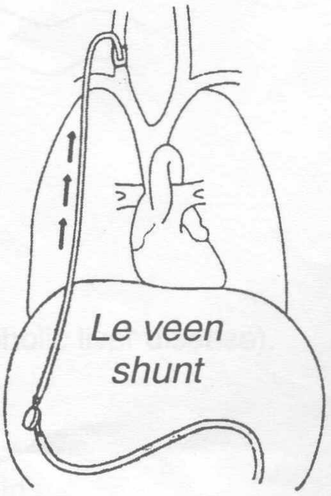
- Salt retention: treated by tight regimen.
- Marked hypoalbuminemia: treated by albumin infusion with adequate dose.
- *Low salt $:* treatment (stop diuretics + fluid restriction for few days and then resume diuretic therapy).
- Malignancy e.g. hepatoma.
- T.B. peritonitis (immunocompromized patient).
- Impaired kidney function.
- Weak or low dose diuretic.

Last lines of treatment:

- ***Le veen shunt:***

  It connects peritoneum to jugular vein by a catheter (subcutaneously).

  Side effects
  - Obstruction.
  - Infection.
  - Volume overload.
  - Electrolyte disturbance.



  Mechanism of Action:

  During inspiration → descent of diaphragm → ↑ intra-abdominal pressure & ↓ intra thoracic pressure (-ve) → allowing passage of the ascitic fluid directly into the circulation.

- ***Ultrafiltration & reinfusion***

  Mechanism of Action:

  Passage of the ascitic fluid outside the body through a hemodialysis machine that can extract the excess water and reintroduce the concentrated fluid through IV set.

  Side effects
  - Peritonitis.
  - Volume over load.

- ***TIPSS (see later):*** TIPSS may lead to encephalopathy (up to 30%) particularly in those with poor liver function: e.g. ↑ PT – ↓albumin, ↑ bilirubin

- ***Liver transplantation***

Q: Refractory ascites (Diuretic resistant ascites)

i.e. Ascites not responding (loss of weight < 200 gm/D) to salt, fluid restriction & (frusemide up to 120-160mg/day+ spironolactone up to 400 mg/day) for at least 2 weeks.

Causes: see the previous causes of resistant or refractory ascites.

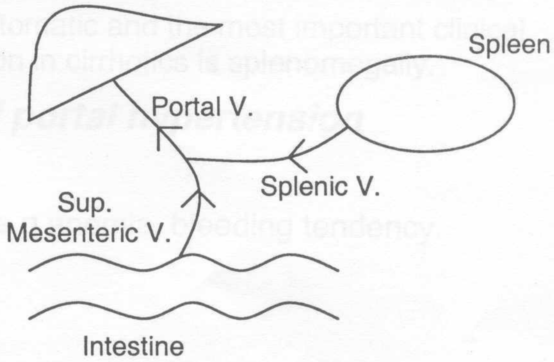
Q: Intractable ascites: (Diuretic intractable ascites)

i.e. Ascites can't be treated by diuretics due to development of diuretic induced complications e.g. encephalopathy.

PORTAL HYPERTENSION

The portal vein is formed by the union of the superior mesenteric and splenic veins. Portal pressure is normally 5-8 mmHg. Portal hypertension means pressure above 10-12 mmHg.

Causes



1- Presinusoidal

- Bilharziasis.
- Primary biliary cirrhosis.
- Portal vein thrombosis.
- Sarcoidosis.
- Congenital hepatic fibrosis.

2- Sinusoidal

- Liver cirrhosis (most common).
- Alcoholic liver disease.

3- Post. Sinusoidal

- Hepatic vein occlusion (Budd Chiari $).
- Central vein occlusion (veno-occlusive & alcoholic liver disease).

4- Overflow ....dynamic causes

- Splenomegaly not due to liver disease.
- A-V fistula between hepatic artery & portal vein.

Humoral factors in portal hypertension due to chronic liver disease

- Increase endothelin (vasoconstrictor).
- Nitric oxide and glucagon are increased leading to peripheral vasodilatation → stimulation of rennin angiotensin → salt retention → maintaining portal hypertension.

Pathophysiology

1- ***Splenic congestion*** → splenomegally with hypersplenism.

2- ***Gastric congestion*** (congestive gastropathy) diagnosed by endoscopy and can lead to haematemesis or anaemia due to chronic blood loss.

3- ***Portosystemic*** Shunts

- Esophageal varices at the gastro-esophageal junction.
- Caput medusae.
- Rectal varices.

4- ***Intestinal congestion.***

5- ***Ascites*** (portal H. is a localizing factor rather than a cause).

If pressure gradient between hepatic and portal venous systems i.e. hepatic venous pressure gradient **(HVPG)** increases to > 10-12 mmHg (normally it is 4mmHg), portosystemic collaterals (varices) may develop. Measurement of HVPG is invasive and rarely necessary to make diagnosis.

Clinical picture

1- Manifestations of the cause

(i.e. manifestation of chronic liver disease for example liver cirrhosis).

2- Manifestations of portal hypertension

Most patients are asymptomatic and the most important clinical sign of portal hypertension in cirrhotics is splenomegally.

3- Manifestations of complication of portal hypertension

- Rupture esophageal varices.
- Pancytopenia (hypersplenism) e.g anemia, bleeding tendency.
- Hepatic encephalopathy.

Investigations

1- Cause

- Liver function tests and other biochemical tests.
- Stool and urine examination for bilharzial ova.

2- Sonar: Increase PV diameter (If > 14 mm = Portal H.), liver cirrhosis, periportal fibrosis.

3- Duplex scan to detect pressure and patency of portal vein.

4- Upper GI endoscopy showing esophageal varices.

5- Barium swallow showing esophageal varices.

6- Biopsy: liver biopsy diagnostic for liver cirrhosis & rectal biopsy for bilharziasis.

Grades of esophageal varices by endoscopy

Grade I: The varices **can** be depressed by endoscoppy

Grade II: The varices **cannot** be depressed by endoscoppy

Grade III: The varices are confluent around the circumference of the esophagus

N.B. Cherry-red spots predicts a high risk of bleeding

Complications of Portal Hypertension:

- Rupture esophageal varices.
- Hypersplenism.
- Renal failure.
- Congestive gastropathy.
- Ascites.
- Hepatic encephalopathy (portosystemic encephalopathy).

Treatment of Rupture Esophageal Varices

Q Indication of treatment of portal hypertension?

- History of bleeding (i.e rupture varices).
- Impending rupture of esophageal varices (by endoscopy)!?.

So, no interference as long as no bleeding !?

I- Medical

1- Shock

1. Blood transfusion.
2. Plasma transfusion.
3. Fluids infusion.
4. Vit K injection.

2- Encephalopathy

1. Enema.
2. Lactulose.
3. GIT antiseptics.

3- Measures to decrease portal Pressure

(1) During attacks of bleeding.

a- Pitressin

Dose: IV drip (20 IU/hour).

Action: Vasospasm in the splanchnic arterioles → ↓ blood flow to intestine → ↓ portal H.

Side effect: Generalized vasospasm, e.g. myocardial infarction, so the addition of nitrates enhance the efficacy of vasopressin.

b- Terlipressin (Glypressin)

Dose: 2 mg/6 hr. IV till hemorrhage stops & then ½ dose for another 24 hrs.

Action: Vasopressin is released from it over several hours to reduce portal pressure without systemic effects (Selective).

c- Octreotide:

50 μg bolus followed by infusion of 50 μg/hr for 48 hrs.

(2) In between attacks

a- Propranolol: given in doses that reduce heart rate by 25%

It reduces portal pressure by splanchnic vasoconstriction and to a lesser extent by reducing cardiac output. It is most effective in compensated liver cirrhosis

Disadvantage: It may make resuscitation more difficult if the patient bleeds.

b- Other drugs

- Nitrates.
- Ca channel blockers.

II- Instrumental Treatment

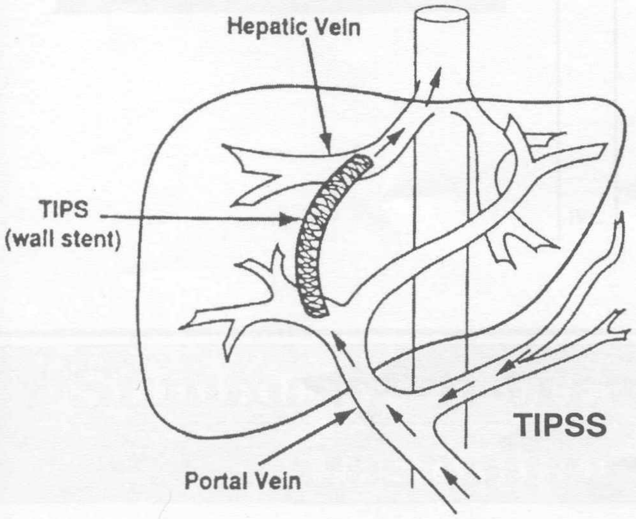
*Injection sclerotherapy (best treatment during emergency)

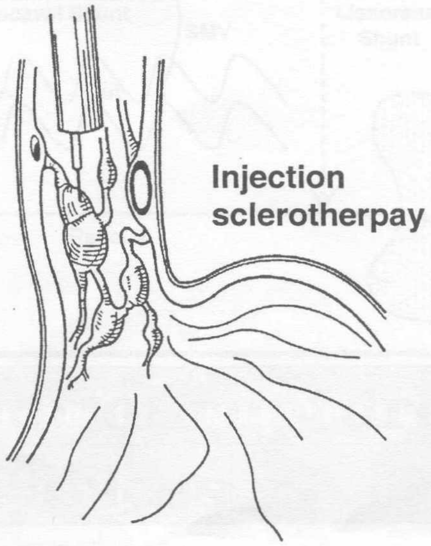
Through an upper endoscopy we inject ethenolamine oleate (old sclerosant) directly into the varix to obliterate its lumen.

Recently injection of bucrylate **(Histoacryl®)** is the best specially for fundal varices.

Complications

- Bleeding.
- Pain.
- Dysphagia (due to fibrosis).
- Infection.





*Sangstaken or Minnesota tube

- Mechanical compression of esophageal varices, if sclerotherapy has failed or is unavailable.
- The tube should be left in place for up to 12 hours, removed in the endoscopy room prior to sclerotherapy.

*Transjugular intahepatic portosystemic stent shunting (TIPSS or TIPS).

(Trans Jugular intra hepatic porto systemic stent shunting) stent placed between the portal vein & the hepatic vein under radiological control via the internal Jugular vein (Radiological intervention), it can be used for acute bleeding not responding to sclerotherapy.

III- Surgical treatment

- Portosystemic shunts (major surgery).
- Splenectomy devascularization (minor surgery).

A) Portosystemic Shunts (High mortality)

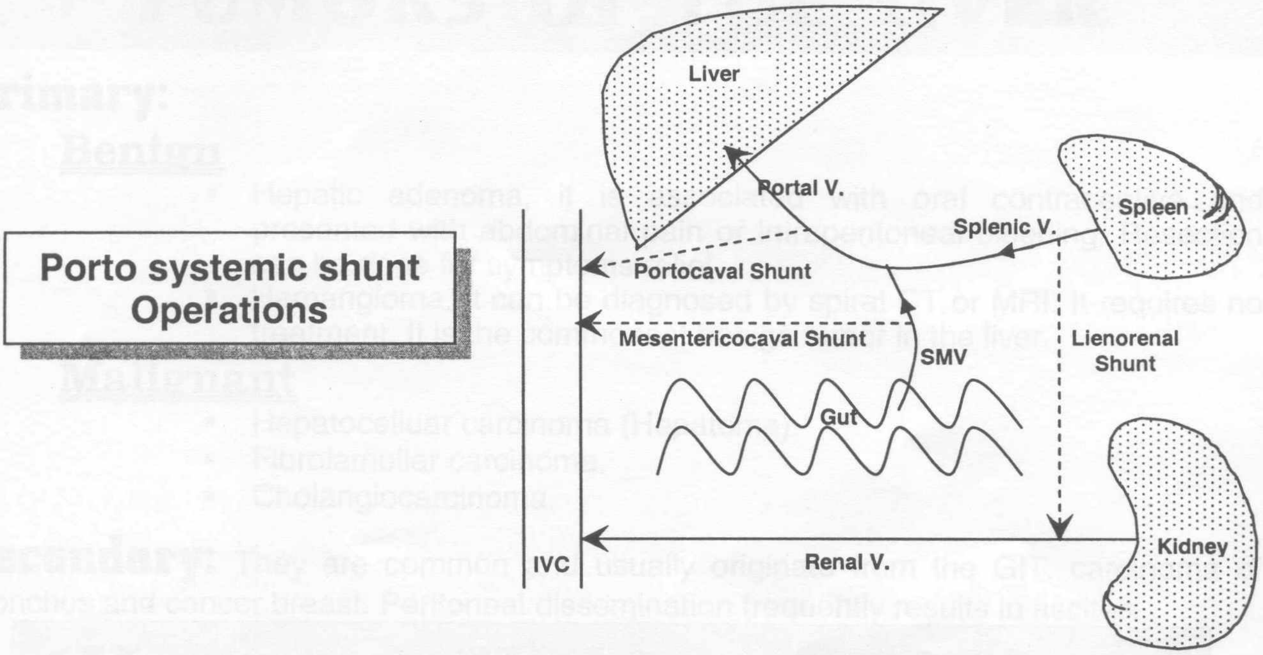
1- Portocaval & mesentericocaval

Advantage → decrease portal H.

Disadvantage → encephalopathy.

2- Lienorenal → minimal encephalopathy, the best **(Warren operation)**.

B) Minor surgery Splenectomy & devascularization = **(Hassab Operation).**



Summary of treatment of rupture Oesophageal Varices

Management of Acute bleeding (during attack)

1. Treatment of shock & encephalopathy

2. Reduction of portal venous pressure

- Vasopressin.
- Terlipressin.
- Somatostatin, it also causes splanchnic vasoconstriction.

3. Local measures

- Sclerotherapy.
- Banding less easy (endoscopic variceal band ligation).
- Balloon tamponade.
- TIPSS
- Esophageal transection with a stapling gun if the above measures fail, it carries the risk of esophageal stenosis.

Prevention of recurrent bleeding (in between attacks)

- Sclerotherapy with follow up.
- Banding.
- Propranolol
- TIPSS
- Portosystemic shunt !?

TUMORS OF THE LIVER

Primary:

Benign

- Hepatic adenoma, it is associated with oral contraceptive and presented with abdominal pain or intraperitoneal bleeding. Resection can be done for symptoms relief.
- Hemangioma, it can be diagnosed by spiral CT or MRI. It requires no treatment. It is the commonest benign tumor in the liver.

Malignant

- Hepatocelluar carcinoma (Hepatoma).
- Fibrolamellar carcinoma.
- Cholangiocarcinoma.

Secondary: They are common and usually originate from the GIT, carcinoma of bronchus and cancer breast. Peritoneal dissemination frequently results in ascites.

(Hepatocellular carcinoma)

Hepatoma

- Hepatocellular carcinoma usually occur in patients with cirrhosis and is common in areas where infection with hepatitis B and C viruses is prevalent. It is a rare complication of autoimmune chronic hepatitis.
- The highest frequency is in the African and oriental races.

Predisposing factors

1- HBV, HCV.
2- Liver cirrhosis especially haemochromatosis and alcoholic cirrhosis (cirrhosis is present in over 80% of cases).
3- Alcohol may be a co-carcinogen with HBV.
4- Aflatoxin, it is a metabolite of a fungus **(Aspergillus flavus)** found in ground nuts. It may lead to mutations in a tumor suppressor gene.
5- Androgenic steroids e.g. Danazole.

Mechanism of hepatoma with HBV & HCV

- HBV DNA integrate with the genome of hepatocyte.
- HCV → cirrhosis → hepatoma (no integration).

Clinical Picture (it is a highly malignant tumor)

Any patient with liver cirrhosis with rapid unexplained deterioration e.g. weight loss, ascites, fever, ….) suspect hepatoma.

1. The liver is enlarged, irregular and tender, hepatic bruit may be audible.
2. Abdominal pain, Jaundice, weight loss, anorexia, fever.
3. Resistant ascites, liver cell failure.
4. ***Paramalignant $ (non metastatic manifestations)***

Due to abnormal peptides secreted from the tumor which may be similar to hormones e.g.

- Insulin like growth factor → hypoglycemia.
- Parathyroid hormone like peptide→ hypercalcemia.
- Erythropiotin → polycythemia.
- Hyperthyroidism due to inappropriate thyroid stimulating hormone production.

Hypoglycemia may be also due to increased demand for glucose by an enormous tumor mass

Investigations

1) ***α fetoproteins*** increased in 85% of cases (up to > 400-500 ng/ml), it is sensitive but not specific.
2) ***Recent tumor marker***: Des-γ-carboxy prothrombin (it is specific but not sensitive)
3) ***Serum ferritin*** increase is due to production of ferritin by the tumour
4) ***Sonar***: focal lesion (Hypo-echoic).
5) ***Liver radioisotope scan*** showing focal area with low uptake.
6) ***CT scan*** showing focal lesion (hypodense lesion).
7) ***Spiral CT:*** can differentiate between benign and malignant masses.
8) ***MRI***, it may differentiate benign from malignant lesions.
9) ***Biopsy***: diagnostic but recently it is better avoided as it may cause seeding of malignant cells.

Treatment

1- Medical (unsatisfactory)

Local cytotoxic drugs

injection into celiac trunk e.g. by doxorubicin or mitomycin C.

Systemic cytotoxic drugs

- Systemic chemotherapy has been widely used, but the response is poor.
- Doxorubicin therapy fail to prolong survival, also it leads to cardiotoxicity.

2- Embolization

with gel foam, this leads to ischemic necrosis of the tumor.

3- Surgery

Surgical resection

Criteria of patients

- Localized tumor.
- Non cirrhotic liver as patients with decompensated cirrhosis are particularly prone to post operative hepatic insufficiency.

Transplantation

Criteria of patient

- Patent hepatic artery and portal vein↓.
- Adequate cardiopulmonary & renal functions.

Liver Transplantation is the procedure of choice in dealing with hepatocellular carcinoma.

Recent non surgical treatment of hepatocellular carcinoma

1- Percutaneous ethanol interstitial tumor injection

It causes coagulative necrosis of tumor cells and thrombosis of tumor vessels and is well tolerated. Survival is better for tumors < 2 cm, solitary with good liver status.

2- Thermoablation with radiofrequency

It is safe and convenient for patients with compensated cirrhosis and small hepatocellular carcinoma.

3- Thermoablation with Laser therapy

Q Fibrolamellar carcinoma of the liver ?

- It is a distinct variant of hepatocellular carcinoma.
- Occurs in young age.
- It is usually present with abdominal pain.
- No risk factors e.g. cirrhosis or hepatitis B or C.
- Negative α fetoprotein, Sonar shows hyper-echoic lesion
- Biopsy shows large polygonal malignant hepatocytes in a dense lamellar fibrous tissue stroma.
- Better prognosis than hepatoma.

Common malignancies ch.ch. by paramalignant $

- Hepatoma.
- Bronchogenic carcinoma.
- Hypernephroma.

Hepatic nodules

Causes

1. Nodular hyperplasia.
2. Adenoma.
3. Haemangioma.
4. Hepatoma.
5. Fibrolamellar carcinoma.
6. Abscess either pyogenic or amoebic.
7. Granulomas (see later).

Nodular regenerative hyperplasia

Small hepatocyte nodules unassociated with fibrosis. It is associated with many conditions such as connective tissue diseases, blood diseases, & steroids therapy, the condition usually presents as an abdominal mass, liver biopsy is diagnostic. Prognosis is good but hepatocellular carcinoma may occur.

Focal nodular hyperplasia

It is a subcapsular liver nodule with central fibrosis. It is almost always asymptomatic.

FATTY LIVER

(HEPATIC STEATOSIS)

Enlargement of liver due to hepatic infiltration with neutral fat

Causes

Macrovesicular

1- Alcohol.
2- Obesity (Excessive intake of carbohydrates & fats).
3- DM (Type II).
4- Total parentral nutrition (TPN).
5- Protein malnutrition.

Microvesicular (Leading to fulminant failure)

1- Acute fatty liver of pregnancy.
2- Reye's $.
3- Tetracycline toxicity.

Clinical picture

- Cause.
- Liver+++, soft. Rounded border sometimes tender.
- Abdominal pain, dyspepsia may occur.
- Fulminant failure in the above causes.

Investigations

- ***Sonar:*** enlarged homogenous liver, it is helpful but not diagnostic.
- ***Cause*** e.g. blood sugar.
- ***Definite diagnosis by biopsy***. (but usually is not needed).
- ***Transaminases*** may be slightly elevated.

Treatment (Treatment of the cause plus) :

- ***Lipotropic drugs:*** e.g. choline.
- Treatment of fulminant failure (see before).

Non alcoholic steatohepatitis (NASH)

- Steatohepatitis is the necro-inflammatory complication of severe persistent hepatic steatosis
- NASH is associated with obesity, D.M. and total parentral nutrition.
- The liver is fatty on biopsy with Mallory bodies.
- The transaminase level is 2-4 fold.
- Prolonged steatohepatitis may lead to cirrhosis.
- ***Treatment*** is with removal of the cause and weight reduction.
- ***NB:*** Excessive alcohol consumption can lead to alcoholic steatohepatitis

Non-alcoholic fatty liver disease **(NAFLD)** is a chronic liver disease with histological features similar to those of alcohol related liver disease. **NASH** constitutes about 20% **of NAFLD** and is part of spectrum of disease.

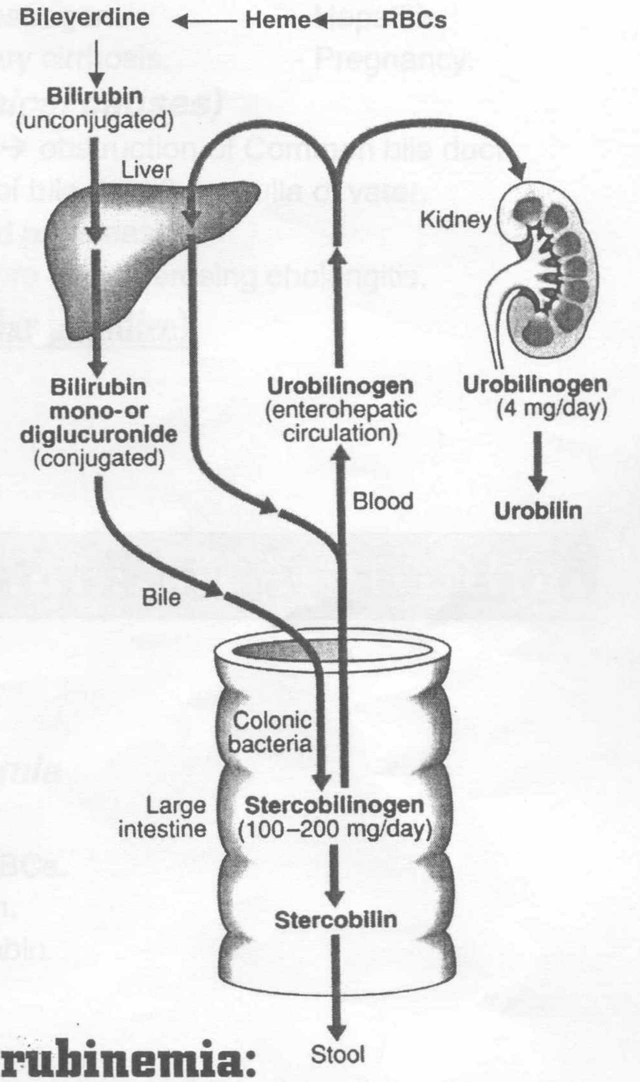
JAUNdICE

This means yellowish discolouration of the skin , mucous membrane and sclera due to hyper-bilrubinemia.

S. bilirubin must be > 2.5-3 mg/dL to give clinical Jaundice.

Bilirubin metabolism

- ***RBCs → heme→ bileverdine → indirect bilirubin.***
- ***The bilirubin passes into three steps.***



Uptake of indirect bilirubin through Y and Z receptors in the liver.

Conjugation and **Secretion**:

Conjugation occurs in the liver by glucouronyl transferease and the conjugated bilirubin is secreted with the bile into the small intestine in the form of stercobilinogen which passing into three directions:

- Part of it enters the enterohepatic circulation.
- Another part escapes to the systemic circulation reaching the kidney and secreted in urine (urobilinogen).
- The last part passes to the large intestine to be transformed into stercobilin.

Causes of indirect hyperbilirubinemia: (Unconjugated hyperbilirubinemia)

Indirect > 80-85% of the total bilirubin.

1- Haemolysis of RBCs (prehepatic jaundice)

2- Uptake defect: Gilbert's syndrome (hereditary).

3- Conjugation defect:

- Crigler-Najjar syndrome.
- Abnormal steroid in maternal milk → inhibit enzyme of conjugation (breast milk jaundice).

Causes of direct hyperbilirubinemia (Conjugated)

(Direct > 50% of the total bilirubin).

Causes

1. Cholestatic jaundice (Obstructive Jaundice)

Intrahepatic

- Drugs e.g. estrogen.
- Primary biliary cirrhosis.
- Hepatitis.
- Pregnancy.

Extrahepatic (mechanical causes)

- Gall stones → obstruction of Common bile duct.
- Carcinoma of bile duct & ampulla of vater.
- Cancer head pancreas.
- Biliary stricture and sclerosing cholangitis.

2. liver cell failure (hepatocellular jaundice)

3. Excretion Defect

- Dubin Johnson $.
- Rotor $.

Hemolytic or prehepatic Jaundice

Causes: Hemolytic Anemia.

Clinical picture

Evidence of Hemolytic anemia

- Anemia.
- Short lifespan of RBCs.
- ↑ Foecal stercobilin.
- ↓ Serum hepatoglobin.
- Reticulocytosis.

Sclera: Lemon yellow.

Urine: No discoloration of urine (it may be reddish due to. haemoglobinuria) so it is called (acholuric jaundice)

Stools: Dark brown.

Investigations

1- Evidence of Haemolysis.

2- Urobilinogen, stercobilin are increased.

3- Bilirubin is usually not > 5 mg/dL as long as the liver is normal if > 5mg (marked ↑↑) = Liver Disease.

Treatment: See hemolytic anemia.

Cholestatic or Obstructive Jaundice

(Cholestasis Or The Syndrome of Cholestatsis)

Cholestasis is defined as interference with bile flow with accumulation of bile in liver cells and biliary passages, this leading to retention of bilirubin and bile acids in the blood

Causes

- Intrahepatic as before.
- Extrahepatic as before.

Clinical Picture

(1) Obstructive Jaundice

- Itching.
- Pain in some cases of cancer head of pancreas or obstruction of CBD e.g. calcular obstruction.
- Weight loss in malignancy.
- **Sclera**: (Olive green).
- **Stool**: clay colour.
- **Urine**: dark colour, and frothy.

(2) Cirrhosis with prolonged cholestasis (biliary cirrhosis)

Investigations

1. Evidence of obstructive jaundice

- ↑ Direct bilirubin, ↓ stercobilin and urobilin.
- Bile salts present in urine → decrease surface tension of urine → frothy urine (yellow froth).
- ↑ Transaminase (mild elevation).
- ↑ Alkaline phosphatase (marked elevation).
- ↑ Serum cholesterol.

2. Cause e.g. ERCP, abdominal sonar.

Treatment

- Medical as before, see primary biliary cirrhosis.
- Surgery for surgical causes.

- Conjugated bilirubin is also found in the blood in unconjugated hyperbilirubinemia, but it doesn't exceed 20% of the total plasma bilirubin and is not sufficient to cause bilirubinuria.
- Prolonged obstructive jaundice → dysfunction of hepatocytes, renal failure and bleeding tendency.
- Obstructive jaundice with oliguria + increased serum creatinine = bilirubin nephropathy, as direct bilirubin leads to acute tubular necrosis.
- In hepatocellular jaundice usually there is an element of intrahepatic cholestasis so, the term cholestatic jaundice can include hepatocellular jaundice (Intrahepatic cholestasis) and obstructive jaundice (extrahepatic cholestasis)

Hepatocellular Jaundice

Cause

- Acute parenchymal liver disease e.g. acute hepatitis.
- Chronic parenchymal liver disease e.g. chronic hepatitis & liver cirrhosis.

Clinical picture

Investigations

Liver cell failure → See before

The limiting step of bilirubin metabolism is excretion (or secretion) so, direct bilirubin is higher than indirect bilirubin.

- Indirect bilirubin increased due to defect in uptake & conjugation.
- Direct bilirubin increased due to defect in secretion.

Congenital non-hemolytic hyperbilirubinemia

Gilbert's Syndrome (the commonest)

Partial & isolated defect in uptake + mild defect in conjugation.

It is an autosomal dominant disease.

It affects 2-5% of the population.

Clinical Picture (it is maily asymptomatic)

1- Second decade of life, males > females.
2- Mild Jaundice, it increases with fasting.
3- Good general condition.
4- No manifestations of hemolytic anemia or liver disease.

Investigations ***(It may be diagnosed by chance at a routine investigation)***

1- S. bilirubin is mildly elevated mainly indirect, not > 6 gm/dL.
2- No evidence of hemolytic anaemia.
3- Normal liver function tests.

Treatment

No need for treatment (normal life span) - phenobarbitone occasionally used.

Grigler-Najjar syndrome

Defect in Conjugation → Jaundice

Type I → Autosomal recessive → kernicterus during infancy.
Type II → Autosomal dominant → can survive to adulthood.

Treatment of type II

Phenobarbitone - liver transplant.

Dubin-Johnson syndrome

Partial defect in excretion.

Autosomal recessive.

Clinical picture

- Jaundice.
- Good general condition.
- Deposition of yellow & brown pigment In hepatocytes.

Investigations

1- Bilirubin: mild elevation of direct bilirubin

2- Biopsy (dark pigment inside hepatocytes), it had been proved to be a metabolite of catecholamines.

3- +ve Bromosulphthalein (BSP) Test:

Normally 90% of this dye is removed from blood within 45 minutes after I.V injection in normal liver. In Dubin-Johnson syndrome there is a late rise in plasma BSP after an initial fall due to reflux of the dye from the liver reflecting hepatic excretion defect.

4- No evidence of obstruction.

5- No evidence of LCF.

Treatment

No treatment (almost normal life span).

Rotor $ like Dubin-Johnson without pigment. It is an autosomal dominant

Familial jaundice	***Recurrent jaundice***
1. Gilbert $.	1. Hemolytic.
2. Grigler Najjar $.	2. Wilson's disease.
3. Dubin Johnson$.	3. Gilbert's.
4. Inherited hemolytic anemia.	4. Cholestasis of pregnancy.
5. Wilson's disease.	5. Gall stones.
6. Hemochromatosis.	6. Periampullary carcinoma.
7. Cholestasis of pregnancy.	

Painful jaundice	***Painless Jaundice***
1. Calcular jaundice (Gall stones).	1. All familial jaundice.
2. Hepatitis.	2. Any type of cirrhosis.
3. Cancer head pancreas	
4. Congested liver	
5. Hepatoma, fibrolamellar carcinoma	

Amoebic liver abscess

Etiology

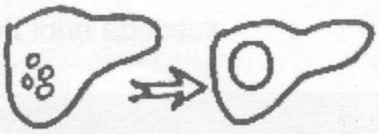
Entamaeba histolytica (vegetative form) carried to the liver from the colon through the portal venous system.

Pathology

Amoeba reach the liver through portal vein tributaries → multiple small cavities due to proteolytic enzymes → fused together → abscess mainly in the right lobe by the streaming effect.

Contents (Anchovy sauce. = Choclate material)

- Necrotic tissue.
- RBCs.
- Leucocytes.
- Amoebae in the wall of the abscess.



Clinical picture

Onset is insidious

1- History of ambiasis

- Diarrhea with dysentery.
- Constipation alternating with diarrhea.

2- Picture simulating hepatitis but there are:

- **Severe pain** in right hypochondrium.
- **Severe toxemia** with nausea & vomiting, rigors & sweating.
- **Tender hepatomegaly ±** mass (cystic).
- **No Jaundice:** its presence means severe infection.
- **Intercostal tenderness**.
- **Tender fist percussion.**

Investigations

1- **Liver biochemistery,** high alkaline phosphatase.
2- **Sonar** → Cyst → Aspiration → Anchovy sauce.
3- **Leucocytosis.**
4- **Raised right diaphragmatic cupula** by X ray.
5- **Rt sided pleural effusion** by X ray.
6- **Amoebic complement fixation test is positive .**

Liver disease with pleural effusion:

1. *Amoebic liver abscess → right sided pleural effusion (exudate).*
2. *Liver cirrhosis + Ascites → right sided pleural effusion (transudate).*
3. *Liver cirrhosis + Ascites with left sided pleural effusion, suspect lung disease e.g. pulmonary T.B. (exudate)*
4. *Liver cirrhosis → bilateral pleural effusion due to hypoproteinemia (transudate).*

Treatment

- ***Flagyl Infusion*** **500mg/8hours** + ***broad spectrum antibiotics*** (3rd generation cephalosporin or quinolones) for 2ry infection. oral flagyl 800 mg thrice daily for 10 days can be used.
- A course of luminal amoebocide e.g diloxanide furoate (fluramide) 500 mg/8hrs for 10 days should be given.
- ***Aspiration***

  Indications
    - Large abscesses.
    - Left lobe abscesses.
    - Impending rupture, as this may lead to:
      - Right pleural effusion.
      - Amoebic pericarditis in cases of left lobe abscess.
      - Rupture into skin.

Q Jaundice + leucocytosis

1. Amoebic liver abscess.
2. Ascending cholangitis.
3. Leptospirosis.
4. Fulminant liver failure.

Bilharziasis

(see tropical diseases)

Pathology

- Bilharzial ova reach liver through PV tributaries → lodged in portal tracts → Inflammatory reaction (granuloma) → Periportal fibrosis around the portal veins → pre - sinusoidal portal hypertension.
- Bilharziasis causes liver fibrosis & not cirrhosis (no loss of architecture).
- Patients with bilharziasis usually develop cirrhosis mostly due to post viral hepatitis cirrhosis. Recently there is a link between bilharziasis & hepatitis C!?

Clinical picture

1- History of bilharziasis.

2- Portal hypertension.

3- LCF is usually late as the hepatic architecture is usually normal but with occurrence of cirrhosis, liver cell failure can occur.

Investigations

1- For bilharziasis (see tropical diseases).

2- Liver function tests.

3- Abdominal sonar.

Treatment

1- Anti Bilharzial drugs (see tropical disease).

2- P.H. – L.C.F.

3- Viral hepatitis if present .

HEPATOTOXIC DRUGS

- ***Acute hepatitis***
  - Halothane.
  - INH, rifampicin.
  - Cytotoxic drugs.
- ***Chronic hepatitis***
  - Methyldopa. - INH.
  - Nitrofurantoin - Fenofibrate.
- ***Cholestasis***
  - Anabolic steroids. - Phenothiazines.
  - Oral contraceptive pills. - Tricyclic antidepressants
  - Oral hypoglycemic.
- ***Fatty liver***
  - Tetracyclines. - Sodium valproate → (anti epileptic).
  - Amiodarone. - Corticosteroids.
- ***Hepatic necrosis***
  - Paracetamol (toxic dose > 15 gm).
  - Carbon tetrachloride. - Amanita mushrooms.
  - Hepatic fibrosis. - Methotrexate. - Vitamine A.
- ***Pelioses hepatis***
  - Anabolic steroids. - Contraceptive pills.
- ***Hypersensitivity***
  - Allopurinol. - Sulfonamides.
  - Antithyroid drugs. - Phenytoin.
  - Diltiazem. - Penicillins.
- ***Budd chiari $*** → contraceptive pills.
- ***Adenoma*** → contraceptive pills, anabolic steroids.
- ***Hepatoma*** → Danazole.

Q Drugs causing Jaundice

Hepatotoxic drugs. - Drugs causing haemolysis.

Mode of hepatic toxicity of important drugs.

- ***Direct toxicity (predictable, dose dependent)***
  - Acetaminophen.
  - Amanita mushroom.
  - Carbon tetrachloride.
- ***Idiosyncratic reaction (unpredictable, dose independent)***
  - Halothane.
  - Isoniazide.
  - Phenytoin.
  - Sodium valproate.

An idiosyncratic drug reaction is a dose independent immune reaction which is based on an individual patient's biochemical alteration of drug metabolism (an abnormal susceptibility to an agent peculiar to an individual).

- ***Both mechanisms!?***
  - Methyl D.
  - INH.
  - Sodium Valproate.

Postoperative jaundice

- Halothane hepatitis.
- Incompatible blood transfusion.
- Missed stone in CBD during cholecystectomy.
- Shock → ischemic injury of the liver.
- Drugs (perioperative).

Spontaneous bacterial peritonitis (SBP)

(It is a precipitating factor of hepatic encephalopathy)

- *It occurs in about 8% of cirrhotics with ascites.*
- *Patient with liver cirrhosis & ascites with marked deterioration without apparent precipitating factor, suspect spontaneous bacterial peritonitis.*
- *The organism gain to the peritoneum by hematogenous spread.*

The incriminated bacteria are E coli, Klebsiella and enterococci .

Clinial Picture

1- Fever, abdominal pain, rebound tenderness.

2- It may be silent. i.e. without fever or abdominal pain.

3- Marked deterioration in patient with liver cirrhosis and ascites.

Investigations

- Culture → E coli, klebsiella.
- WBCs count in ascitic fluid > 500/m^3 or > 250 PNL/m^3.

Treatment:

- Antibiotic (cefotaxime) 3rd generation cephalosporines 2-4 gm/d for about one week.
- Recurrence is common, norfloxacine can be used for prevention.

Vascular Liver Diseases

(1) Portal vein thrombosis

Causes

1- Blood disease e.g. polycythemia.
2- Pancreatic tumor and hepatoma may invade and compress the portal vein.
3- Umbilical sepsis.
4- Postoperative, commonly after splenectomy.

Clinical Picture

- Portal hypertension with bleeding from oesophageal varices.
- The spleen is usually enlarged.
- The liver is normal in size and consistency.
- Ascites is early and transient, (it is usually subsides as the collateral circulation develops). Ascites is usually related to an additional factor which has depressed the liver function e.g haemorrhage.

Investigations

- Duplex scan.
- Liver histology is normal.

Treatment (any underlying cause must be identified and treated)

As portal hypertension, but surgery is difficult due to absence of patent veins for portal - systemic shunts.

(2) Budd–Chiari $

Hepatic vein occlusion, & sometimes the IVC.

Causes

1- Oral c.c. pills.
2- Polycythaemia.
3- Hyper coagulable states e.g. Protein C & S deficiency.

Diagnosis

1- Abdominal pain.
2- Tender hepatomegally.
3- Ascites + portal hypertension.
4- LL edema with IVC obstruction.
5- Negative hepatojugular reflux.

Investigations

- Duplex scan.

Treatment

- Treatment of the cause.
- In recent cases we can use streptokinase then heparin.
- Short hepatic venons strictures can be treated with angioplasty, more extensive hepatic vein obstruction can be treated with TIPSS.
- Side to side portocaval shunts may be of value, or Le veen shunt for ascites !?

DD of enlarged tender liver (tender hepatomegally)

1. Hepatitis → enzymes, markers,.....
2. Hepatic amoebiasis → U/S,.....
3. Fatty liver → U/S......
4. Hepatoma → U/S, AFP,......
5. Congested liver:
    a. Right sided heart failure → congested neck vein, LL edema,....
    b. Budd-Chiari $ → no congested neck veins

(3) Veno-occlusive disease

- Widespread non thrombotic occlusion of central hepatic venules. It is a small vessel disease (variant of Budd Chiari $).
- Patients with alcoholic Liver disease may show hepatic venule sclerosis or occlusion.

Causes

- Cytotoxic drugs.
- Irradiation.
- Heliotropium plants to make tea.

Clinical Picture as Budd Chiari $.

Treatment

- It is mainly supportive with control of ascites and liver cell failure.

(4) Cardiac disease

- Hepatic injury, due to congestion may occur in right heart failure or in constrictive pericarditis, clinical features are usually dominated by the cardiac disease. Long standing cases may developed cardiac cirrhosis (rare).
- Acute heart failure may lead to a picture similar to acute hepatitis due to reduction in hepatic perfusion **(shock liver).** The patient becomes very ill with enlarged tender liver, jaundice with very high transaminases.

(5) Hepatic arterial disease

- Hepatic artery occlusion may be caused by emboli, PAN, trauma, irradiation or neoplasm.
- Severe upper abdominal pain usually occur with elevated transaminases.

Q Congestive Gastropathy

- Long standing portal hypertension causes chronic gastric congestion which leads to punctate erythema diagnosed by endoscopy.
- Acute bleeding can occur but repeated minor bleeding causing iron deficiency anemia can occur.
- ***Treatment***: iron – inderal – TIPSS.

Hepatic mitochondrial injury syndromes

- Fatty liver of pregnancy.
- Tetracycline, valproic acid.
- Reye's syndrome.
- Aflatoxine.

These syndromes lead to inhibition of B oxidation of fatty acids leading to fatal microsteatosis.

Liver transplantation

Orthotopic liver transplantation, is the replacement of a diseased liver by healthy organ from a recently brain dead individual. Split liver transplantation (the left lobe) can be used for children, also it can be used if there is no available cadaver.

Indications

= Severe irreversible liver disease for which medical or surgical trials have been exhausted.

1. **Acute liver disease** with fulminant failure.
2. **Chronic liver disease :**

   All patients with end stage (child's grade C) cirrhosis should be considered for transplantation :

   - **Chronic hepatitis B** if HBV-DNA negative, recurrence can occur despite use of HBIG and lamivudine.
   - **Chronic hepatitis C,** prognosis of the graft is good despite HCV reinfection. Cirrhosis occurs in 10-20% within 5 years, antiviral therapy may delay the disease.
   - **Autoimmune hepatitis** not responding to treatment or have major side effects of corticosteroide therapy.
   - **Alcoholic liver disease** in patients who have stopped drinking without improvement of liver disease.

- **Wilson's disease,** hereditary haemochromatosis, α1 antitrypsin deficiency.
- Biliary atresia, sclerosing cholangitis, Budd chiari $.

Contraindications

- Threatening systemic infection.
- Pre-existing cardiovascular or pulmonary disease.
- Metastatic complications.
- AIDS

Pre-operative

- Patent hepatic artery & portal vein.
- ABO blood grouping.
- HLA typing.
- Adequate cardiopulmonary & renal functions.

Post-operative

Immuno suppression to prevent graft rejection by:

- Cyclosporine.
- Tacrolimus - corticosteroids
- Patients require life long immunosuppressive drugs, the doses can be reduced overtime.

Auxiliary liver transplantation

It is a Liver transplantation which is done in cases of fulminant hepatic failure to provide viable liver function by the graft till recovery of the native liver & then we remove the graft (auxiliary liver).

Value

- Short term cytotoxic drugs.
- Preservation of the native liver.

Method

The native liver is left in place and the liver graft placed alongside the native liver.

Rejection

- **Acute or cellular rejection occurs** within 5-10 days post transplant. It may be asymptomatic or presented with fever. It is usually responding to immunosuppressive agents.
- **Chronic ductopenic rejection** is seen from 6 weeks to 9 months post transplant with disappearance of bile duct **(vanishing bile duct $)** with arteriopathy (occlusion of arteries).
- Early cases rarely can be reversed by immunosuppression and retransplantation may be required.

DISEASES ASSOCIATED WITH HEPATIC GRANULOMAS

Hepatic granulomas are usually asymptomatic, however the disorder causing the granuloma may produce extrahepatic manifestations and/or hepatic inflammation, fibrosis and portal hypertension, diagnosis is based on biopsy. Treatment is determined by the underlying disorder.

Causes:

Infections

- Tuberculosis.
- Brucellosis.
- Leprosy.
- Syphilis. (Heparlobatum)
- CMV.
- Bilharziasis.
- Toxoplasmosis.
- Ambebiasis.
- IMN.
- Actinomycosis

Hepatobiliary disorders

- Primary biliary cirrhosis.
- Granulomatous hepatitis.

Systemic disorders

- Sarcoidosis.
- Inflammatory bowel disease
- Lymphoma.

Drugs

- Allopurinol.
- Hydralazine.
- Phenytoin.
- Nitrofurantion.

HEPATIC CYSTS

Non parasitic

- Most of them are congenital.
- They are asymptomatic.
- Abdominal pain, palpable cyst or Jaundice may occur.

Other non parasitic cysts include traumatic & neoplastic cysts.

Parasitic cysts

These cysts are caused by echinococcus granulosus. They can be single or multiple, chronic cysts become calcified. There is abdominal pain or mass, eosinophilia and radiograph showing calcification, surgical removal of the intact cyst after sterilization with alcohol or formalin is necessary.

LIVER & PREGNANCY

Pregnancy does not necessarily exacerbate established liver disease, but it is uncommon for women with advanced liver disease to conceive.

- **Hepatitis A** can be acquired by contact with the excreta of older children. Exposed pregnant women should receive immunoglobulin and vaccine immediately.
- Pregnant women in close contact with persons carrying **hepatitis B** must receive hepatitis B vaccine, which is safe in pregnancy and also hepatitis B immunoglobulin.
- Transplacental transmission of viral **HB, HC** can occur.
- **Hepatitis E** during pregnancy may lead to fulminant liver failure.
- **Gall stone** can occur because during pregnancy the bile becomes more lithogenic and gall bladder emptying is impaired. Cholecystectomy, whether by open operation or laparoscopic is safe during pregnancy.

There are four important specific disturbances of liver during pregnancy:

A) Cholestasis of pregnancy:

- This is an inherited susceptibility of the liver cells to oestrogens, pruritus is the dominant symptom.
- Itching starts in the third trimester of pregnancy & remits within about 2 weeks of delivery.
- Pruritus can be relieved with cholestyramine.
- Usually there is no harm to the fetus.
- Recurrence in subsequent pregnancies may occur.
- There is increase of alkaline phosphatase and bilirubin, also transaminases may be elevated.
- Prognosis is good.

B) HELLP syndrome (with severe case of pre-eclampsia):

The syndrome is consists of:

- Haemolysis.
- Elevated liver transaminases and low platelets.

Delivery is the best treatment for eclampsia.

C) Acute fatty liver of pregnancy:

- It presents in the last trimester with symptoms of fulminant failure.
- Immediate delivery of the child may save both baby and mother.

D) Hyperemesis gravidarum:

It may lead to hepatic dysfunction with jaundice, this resolves when vomiting subsides.

- Pregnancy is not contraindicated in those with well treated Wilson's disease, penicillamine is not harmful to the fetus.
- Primary biliary cirrhosis may present as cholestatic jaundice during, or shortly after pregnancy.
- Pregnancy in liver transplant recipients can be allowed after 1 year post transplant if the condition of the graft is stable.

EXTRAHEPATIC MANIFESTATIONS of LIVER DISEASES

Cardiovascular manifestations:

3. L.C.F leading to hyperdynamic circulation. Also, may leads to hypotension due to vasodilatation.
4. Haemochromatosis leading to cardiomyopathy.
5. Amoebic liver abscess may be complicated by amoebic pericarditis.

Pulmonary manifestations:

6. L.C.F leading to opening of intrapulmonary shunts → hypoxia and cyanosis (hepatopulmonary $).
7. Ascites leading to right sided pleural effusion.
8. Amoebic liver abscess may leads to right pleural effusion.

Hematological manifestations:

9. Chronic liver disease may lead to anemia, coagulation defect and thrombocytopenia (see before).
10. Autoimmune hepatitis and 1ry biliary cirrhosis may be associated with autoimmune Hemolytic anemia
11. Wilson's disease may leads to hemolytic anemia.
12. Hepatitis B → aplastic anemia or Henoch Schonlin purpura.

Renal manifestations:

13. Hepatitis B → membranous G.N.
14. Hepatitis C → membranoproliferative G.N.
15. Liver cirrhosis may be associated with Ig A nephropathy.
16. L.C.F may be complicated by hepatorenal failure.

Rheumatological manifestations:

17. Hepatitis B & C may lead to arthropathy and polyarteritis nodosa.
18. Wilson's disease and haemochromatosis may be associated with chondrocalcinosis.
19. Lupoid, 1ry biliary cirrhosis may be associated with arthropathy.
20. Liver cirrhosis specially 1ry biliary may lead to hepatic osteodystrophy.

Neurological manifestations:

21. Hepatic encephalopathy leads to complex neuropsychiatric manifestations.
22. Wilson's disease may lead to extrapyramidal manifestations.

Endocrinal manifestations:

23. L.C.F (see before).
24. Primary biliary cirrhosis and lupoid hepatitis may be associated with thyroiditis.
25. Haemochromatosis usually affecting the pancreas → D.M..
26. Hepatoma may leads to hypoglycemia.

Skin manifestations:

27. L.C.F leading to skin manifestations e.g. spider naevi, palmar erythema
28. Cholestasis e.g 1ry biliary cirrhosis leading to itching.
29. Haemochromatosis usually associated with hyperpigmentations.
30. Hepatitis C may be associated with lichen planus.

Ocular manifestations:

31. Wilson's disease leading to Kayser Fleischer ring.
32. Liver disease usually leading to jaundice.
33. Primary biliary cirrhosis may be associated with sicca syndrome.

IMMUNE MEDIATED LIVER DISEASES

(1) Autoimmune hepatitis e.g. (lupoid).
(2) Idiosyncratic drug reactions e.g. INH, α-methyl dopa.
(3) 1ry biliary cirrhosis.
(4) Graft rejection.

INHERITED LIVER DISEASES

(1) α1-antitrypsin deficiency.
(2) Gilbert's disease.
(3) Rotor's $.
(4) Dubin Johnson $.
(5) Grigler Najjar $.
(6) Wilson's disease.
(7) Haemochromatosis.

LIVER EMERGENCIES

(1) Hepatic encephalopathy with its types.
(2) Rupture varices.
(3) Emergency immunization for contacts with cases of viral hepatitis.
(4) Graft rejection.

Liver Involvement in Systemic Disease

1- **D.M.**:
   Type I → Glycogen infiltration.
   Type II → fatty liver.
2- **Rheumatoid disease**: drug hepatotoxicity, amyloidosis.
3- **SLE**: hepatic arteritis, chronic hepatitis (rare).
4- **Still's disease**: hepatomegally.
5- **Felty's syndrome**: hepatomegally, nodular hyperplasia.
6- **Sjogren's syndrome**: 1ry biliary cirrhosis.
7- **Scleroderma**: 1ry biliary cirrhosis especially with CREST syndrome.
8- **Leukemia & lymphoma**: hepatomegally.
9- **Glycogen storage disease**: hepatomegally.
10- **Cystic fibrosis**: hepatic cysts.
11- **Haemochromatosis and Wilson's disease**
12- **Sarcoidosis:** liver granuloma
13- **Alpha 1 antitrypsine deficiency:** cirrhosis and pulmonary emphysema

***N.B.:* Drug hepatotoxicity may occur as a result of treatment of any systemic disease**

Different Classifications of Jaundice

I) Hemolytic, obstructive, hepatocellular jaundice (see before).

II) Conjugated, unconjugated jaundice (see before).

III)

- ***Prehepatic i.e. hemolytic.***
- ***Hepatic:***
  1- Congenital non hemolytic e.g. Gilbert's, Dubin Johnson, Rotor and Crigler Najjar syndromes.
  2- L.C.F. and cirrhosis.
  3- Hepatitis.
- ***Post hepatic (obstructive or surgical jaundice):***
  1- Gall stone.
  2- Cancer pancreas.

IV)

- ***Hemolytic jaundice.***
- ***Congenital non hemolytic jaundice:***
  a) Unconjugated:
    - Gilbert's syndrome.
    - Grigler Najjar syndrome.
  b) Conjugated:
    - Dubin Johnson syndrome.
    - Rotor syndrome.
- ***Cholestatic jaundice:***
  a) Intrahepatic:
    - Hepatitis.
    - Cirrhosis.
    - Pregnancy.
  b) Extrahepatic:
    - Gall stones.
    - Cancer pancreas.
    - Sclerosing cholangitis.

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    - Chest.
    - Abdomen.
    - Neurology.
    - General.

حقوق الطبع محفوظة للمؤلف

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